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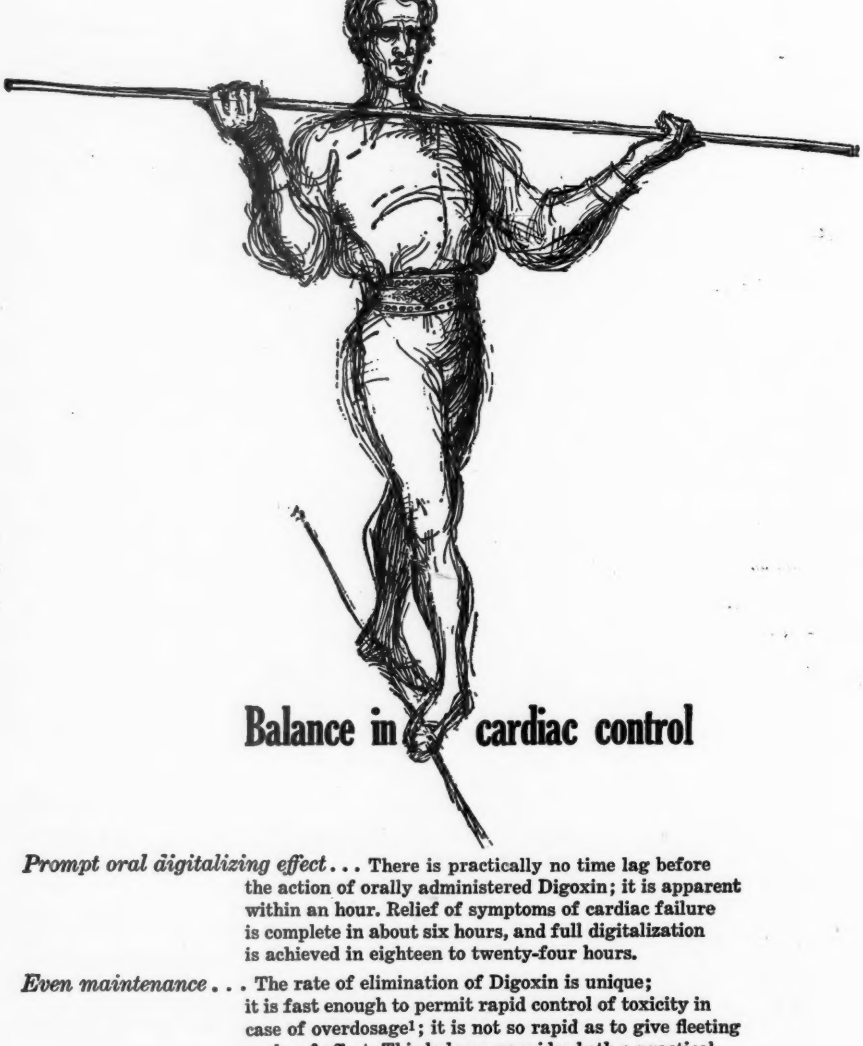

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1. Schaaf, R. S., Hurst, J. W., and Williams C.: Med. Clin. North America (Mass. Gen. Hosp. No.) p. 1255 (Sept.) 1949.

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ANTERIOR-ROOTLET RHIZOTOMY*

A Method of Controlling Spasm with Retention of Voluntary Motion

DONALD MUNRO, M.D.†

BOSTON

THE treatment of paralyzing spasms that prevent the use of any remaining voluntary motor activity of the spastic limb is a notorious neurosurgical and orthopedic failure. Since the potential use of such a limb may be close to normal and, in any event, may be at least partially recoverable through exercises and other physiotherapeutic therapy that is impossible in the presence of spasms, some method of relieving the spasm and at the same time preserving controlled voluntary motion is fundamental to its success. This paper is a preliminary report of what appears to be such a method. It is reported in the hope that increased use will perfect its application and thus bring some measure of hitherto unattainable relief to certain spastic paralytics.

The type of spasm that paralyzes without destroying voluntary motion in a limb is seen in its most characteristic form in patients with partial injuries of the spinal cord. It also occurs as a spastic quadriplegia or diplegia in children who are suffering from the late results of birth injuries. I do not propose to discuss the physiologic explanation of this phenomenon except to say that it is in dispute. At least one point of view, however, is that the basic mechanical factor is a discrepancy between the motor response that is produced and the sensory stimulus that produces it. This discrepancy results in oversensitivity and overactivity of the muscles, — particularly the anti-gravity groups, — to minimal sensory stimuli — especially if the stimulus is a noxious one. Thus the condition of patients with adductor-flexor deformities will be made worse by such attempts at correction as massage, forcible active motion, assisted exercises, muscle training and so forth. It makes no difference whether the movement is active or passive, self-initiated or not. This kind of spasm is not limited to the adductor-flexor type but may also occur in the form of adductor-extensor or alternating extensor and flexor spasm. I have never seen *abductor* spasms in such patients, nor am I familiar with any report of them.

In patients with injuries of the spinal cord this type of spasm is not limited to the somatic musculature; it also involves the visceral muscles and their splanchnic nerve supply. It is seen in its purest form as spasm of the detrusor muscle and of the external urethral sphincter of the urinary bladder. It is also demonstrable as vasospasm in certain peripheral injuries. These are grouped under the general name of causalgia and include Volkmann's contracture and segmental arterial spasm.

Treatment of this condition has been of four types, all of which have been designed to produce repeated temporary or permanent denervation of the spastic muscle or muscles. The methods used have been either surgical or chemical; their purpose is to produce the denervation at either the peripheral-nerve or spinal-cord level. The Stoeffel operation is the prototype of the surgical methods and the repeated procaine injections of one internal pudic nerve exemplifies the chemical methods, both being used at the peripheral-nerve level. The purpose of these methods is to produce some type of denervation of a *single muscle*. The injection method has proved particularly effective in the visceral field but is limited to it.

Other procedures have been designed and used to produce partial or total denervation of *spastic muscle groups* at the level of the segmental portion of the central nervous system. These methods vary from the production of spinal anesthesia to the division of many posterior roots as described by Foerster; they include autonomic ganglionectomy as well as paraspinal injection of the autonomic nervous system or of spinal roots with procaine or alcohol. Examples of these procedures are the repeated procaine injections of the sacral roots for the control of detrusor spasm and injection and surgical ganglionectomy of the sympathetic paravertebral ganglionated chain for vasospasm.

The third kind of therapy is based on the relief of spasm by the production of a state of exhaustion in the spastic muscles; the fourth, by endeavoring

*Presented at the annual meeting of the New England Surgical Society, York Harbor, Maine, September 21, 1951.

†Assistant professor of neurosurgery, Harvard Medical School: surgeon-in-chief, Department of Neurosurgery, Boston City Hospital.

through general physical training to re-establish central control of the excessive motor response by reopening old neural pathways as well as by using and building new ones, in the hope that inhibitory impulses will travel peripherally from the suprasegmental central nervous system. This fourth method is obviously supplementary rather than fundamental in character.

None of these methods have proved entirely satisfactory except in the splanchnic area. This has been especially true in patients with spinal spastic involvement. The Stoeffel procedure, whether done with a knife or by injection, is too narrow in scope and too inaccurate. I have seen it tried several times and, except for the immediate postoperative loss of spasm due to the insult to the incised nerve, it has been a failure in every case. Widespread intraspinal division of the posterior roots has also been a failure, not only in alleviating the spasm but even in relieving pain. Indeed, its failure in these two fields is now so notorious that it should be abandoned in the treatment of these conditions.

A reasonable conclusion to draw from these experiences is that methods aimed at relieving somatic muscular spasm by reduction of the number of sensory stimuli that reach the spastic muscles are not effective. It is further apparent that total permanent denervation of spastic muscles is not suitable either, because not only is the spasm permanently destroyed but so also is all voluntary motor activity. Although this may be desirable and even lifesaving in the presence of a proved transected spinal cord, it is never justified in the presence of a partial cord injury or unless the presence of the transection has been verified by either adequate clinical observation or, preferably, by electrical stimulation above and below the damaged portion of the exposed cord. Such a procedure, therefore, as an anterior dorsolumbar rhizotomy is not suitable for use in the type of spasm under discussion. On the other hand, temporary chemical denervation, whether of the spinal roots or of the peripheral nerves, is suitable and successful provided that the splanchnic rather than the somatic musculature is being treated — and provided also that the motor rather than the sensory nerve supply is injected. This is particularly true in regard to spasm of the bladder and only slightly less so in regard to vasospasm. Such injections, however, are virtually a failure when the somatic musculature is involved. Relief of spasm by the production of muscular exhaustion is so obviously futile as not to merit serious discussion.

In summary, then, it may be stated that control of spasm of visceral musculature can be satisfactorily established by repeated intermittent chemical denervation at the spinal root, the paraspinal ganglionated chain and the peripheral nerve levels, provided that the injection is designed to break the reflex arc on the motor and not the sensory side. On the other hand, relief of spasm of somatic nonvisceral musculature, whether on a permanent surgical or an intermittent chemical basis, has been a failure so far. It should be noted, however, that all attempts to establish control in this field have been directed toward the sensory rather than the motor side of the reflex arc. Other methods presently in use are supplemental in their nature and as such are dependent for their ultimate effect on more fundamental physiologic alterations than are within their scope. Within these limits, however, their use is invaluable and indisputable.

In the light of these experiences, and because of the urgent need for effective treatment of a veteran quadriparetic patient, it occurred to me that the problem of relief of spasm might be approached at the spinal-rootlet level and on the motor side of the reflex arc. This would permit dealing with groups of muscles and by alternate division of motor rootlets would prevent total voluntary paralysis and at the same time reduce the number of motor impulses that could reach the oversensitive muscles. Furthermore, if successful, it would not only permit the use but would facilitate the effectiveness of the auxiliary methods mentioned previously.

This procedure has now been carried out in 3 patients. Two patients had had injuries to the cervical spinal cord; the operation was performed on one to relieve pain and on the other in an attempt to increase the usefulness of the patient's right arm. The third operation was a dorsolumbar one and was done in the hope of increasing the mobility and raising the physical educational level of a child of two years with a cerebral spastic paralysis of both legs due to a birth injury.

The results in the 2 patients with injured cervical cords were satisfactory. In one there was complete and permanent relief of pain and some slight increase in mobility but no increase in usefulness of the arm whose nerve supply had been altered. This improvement, slight as it was, was the more welcome because a Stoeffel-type operation performed about one year earlier on the other and less damaged arm had been a failure. The relief has persisted to date — a matter of three years. In the other patient, the operation has been performed too recently to permit definite conclusions. It is easily demonstrable, however, at the end of two and a half months, that the patient's comfort is increased, his spasm, though still present, is less and the effectiveness of physiotherapeutic treatment for increasing the use of his right arm is greatly enhanced.

The results in the third case have been spectacular. The patient has improved physically, intellectually and psychologically. He has gained, in the three months since the postoperative resumption of physical training, what would have required under other circumstances at least two years. Formerly a bedridden, virtually speechless and helpless little boy, he can now stand and walk with prac-

tically no support; he talks, responds to training and will very likely be rehabilitable to an unexpected degree.

At the operation every other or every third rootlet of the designated roots, whether cervical or dorsolumbosacral, is cut. Before and during section the roots are identified by electrical stimulation. In addition, before section, the minimum voltage required to produce peripheral muscular contractions in the arm or leg is determined by intra-arachnoid stimulation of the anterior surface of the cord above each pair of roots. This is recorded. The same information is obtained and recorded after the rootlet section. A comparison of the two voltage levels is thought to indicate roughly the amount of diminution of innervation that has been effected. After the rootlet section and hemostasis the wound, including the dura, is closed in layers without drainage.

The operation is technically not difficult, although it is less simple in the neck than in the dorsolumbar region. In the cases reported herewith the amount of stimulation, as measured by the minimum voltage necessary to cause peripheral motor contractions, was markedly increased with division of either one half or one third of the rootlets. We may conclude, therefore, that an equivalent number of motor impulses have been thus cut off from the periphery even though the sensory stimuli have remained unchanged. Theoretically, this should reduce the peripheral spasm, maintain voluntary control and permit increased use of the limb.

Case Reports

Case 1. H. K. F., a 26-year-old man, was wounded in military action in April, 1945. He was struck by multiple metallic fragments from an exploding land mine and was immediately and completely paralyzed from the neck downward. Almost at once, however, sensation began to return, and the sensory level descended to the umbilicus. By November, 1945, he was able to walk again, though with difficulty because of spasm in his legs. His arms and hands, both of which had been spastic and held in flexion, were slightly less so at this time. Within the limits of the spasm there was some voluntary motion in both arms, although how much was not certain. By October, 1945, he had acquired normal bladder and bowel control. He was admitted to the Cushing Veterans Administration Hospital, where I saw him on October 1, 1946. At that time his sensation was normal everywhere and all lower-extremity motions were possible though restricted about 50 per cent because of spasticity and stiffness of the joints. The arms could not be voluntarily moved at either shoulder or elbow — and only slightly in the wrist and fingers. The patient could walk but could not feed himself. There was severe bilateral upper-extremity pain and muscular spasm, with an unknown degree of voluntary motion underlying these manifestations.

In December, 1948, the rootlet operation first suggested by me in November, 1947, was carried out after careful consideration of all the factors involved — and after two years of persistent expert but unsuccessful physiotherapy and exercises. A cervical laminectomy was performed in order, if possible, to perform a rootlet operation, decompress the cervical cord and correct the new subarachnoid block that was known to be present. The cord was found to be atrophied, with a syrinx in its center, and strongly adherent to the arachnoid, which adhered to the dura. The roots on both sides were also involved in the scar but were not compressed. The 5th, 6th and 7th roots were isolated on the left. Electrical stimulation of the anterior portion of the uppermost root caused contractions in the left arm. Half the rootlets of this anterior root were cut. Stimulation of the next lowest anterior root caused contraction in the left hand and 2 of its 4 rootlets were cut. The lowest of the 3 anterior roots was then separated and all its rootlets cut after stimulation. Stimulation of the root next above the uppermost root of the three caused spasm of the diaphragm and was considered to be the 4th cervical root. The wound, including the dura, was closed in layers without drainage.

At the end of the eighth postoperative day the patient was able to abduct his left arm at his shoulder to 60° beyond the vertical. He could also adduct at this same joint to about 10° and extend to about 40° beyond the vertical. Rotation of the shoulder was minimal. The elbow rested naturally extended 5° beyond the right angle. It could be flexed to 5°. All motions were now completely painless. There was no spasm of the biceps group of muscles, and the fingers were loose and not spastic. The most striking result was the total absence of all spasm, even in the presence of forced motion, and the complete absence of the previous pain, which, by its constant presence before the operation and its exaggeration even with passive motion, had precluded any effective physiotherapy.

Figure 1. *Case 2: Spasm of Both Hands Prior to Rootlet Operation.*

Previous procedures, none of which had afforded any relief, had been a stellate block with 10 cc. of 1 per cent Cobefrin, direct injection of the left ulnar nerve with 5 cc. of 1.5 per cent Pontocaine (the latter greatly reduced the spasm but did not relieve the pain) and 100 units of curare, which gave no relief of spasm. A cervical myelogram made in January, 1946, was negative. Electromyograms of the right arm made in April, 1946, were interpreted at that time as abnormal

and as showing "irregular involuntary discharge of the neuromuscular unit." In January, 1947, I had explored the patient's cervical cord and demonstrated that there was no subarachnoid block but some atrophy of the cord. Peripheral paralysis and spasm were maximal at this time. In January, 1948, a Stoeffel operation was performed by another surgeon on the right musculocutaneous nerve.

In January, 1949, there was no pain and no muscle spasm in the left arm on which the rootlet operation had been performed. The patient was capable of voluntary motion of the triceps and some of the scapular muscles, but there was none elsewhere, and no muscular atrophy. The right arm, — the one on which the Stoeffel operation was performed, — had returned to its preoperative condition, being generally spastic with a minimal amount of voluntary motion and an ankylosed elbow joint. In September, 1951, this condition was essentially as it was in January, 1949.

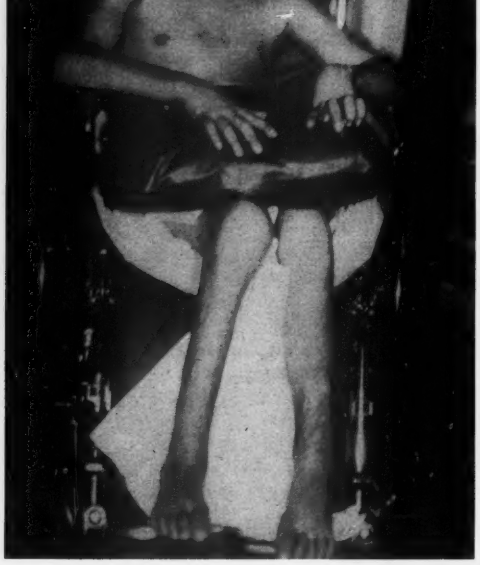

FIGURE 2. *Case 2: Six Weeks after the Rootlet Operation on the Right and Twelve Weeks after the Rootlet Operation on the Left.*

CASE 2. P. de S., a 13-year-old boy, was admitted to the Boston City Hospital on May 8, 1950. In December, 1948, he had sustained an injury to his cervical spine and cord as the result of diving into an empty swimming-pool. A laminectomy was performed by the local surgeon some time later and "adhesions and some degeneration of the cervical cord" were said to have been found. At this time severe adductor-flexor spasm of the legs, arms, hands and fingers was already present, as well as a flaccid scoliosis of the spine when the patient sat erect. Two weeks after the laminectomy alcohol was injected intrathecally about the cauda equina but failed to relieve the spasms. In the subsequent interval, prior to his admission to the Boston City Hospital, he suffered from many decubitus ulcers, developed a perineal urethral fistula and had repeated severe attacks of upper- and lower-urinary-tract infection. In August, 1949, a cystostomy was performed, with great improvement in the patient's condition and healing of the decubitus ulcers. In the following month, however, a periurethral abscess formed; it was drained and caused the perineal fistula. The patient is said to have had congenital heart disease, but the details are not known.

Physical examination on admission revealed a "machine-like" cardiac murmur in the third right and left intercostal spaces, a draining suprapubic cystostomy, a draining perineal urethral fistula, the scars of many bed sores, chronic pyelitis, a contracted, irritable infected bladder filled with many small stones, and numerous calculi in the pelves and calyces of both kidneys. All four extremities were held in adductor-flexor spasm, which was aggravated by active or attempted passive motion and complicated by permanent contractures at both hips and knees and by posterior dislocation of both tibias. There was potentially useful voluntary motion in both arms, forearms and wrists and possibly in the fingers, but no useful voluntary motion could be demonstrated in the legs. On June 6, 1950, a typical anterior dorsolumbar rhizotomy was performed, with immediate consequent loss of all spasm and what little voluntary motion remained in the legs. On August 6, 1950, 2 stones were removed from the left ureter and on September 28, 1950, a single stone was removed from the pelvis of the right kidney. One stone was yet to be removed from the pelvis of his left kidney. In October the patient was out of bed and in a wheelchair. There had been no change in the amount of arm spasm. In November a successful procaine block of the left brachial plexus failed to alleviate the arm spasm. A similar left-ulnar-nerve block at the elbow was equally unsuccessful. The patient

FIGURE 3. *Case 3: Spasm of Both Legs and Feet Prior to Rootlet Operation.*

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continued to have intermittent attacks of acute pyelitis, and in December, 1950, the first attempt was made to close the perineal urinary fistula. This failed. On February 26, 1951, the renal stone was removed from the pelvis of the left kidney.

On April 24, 1951 (Fig. 1), a rootlet operation was performed on the 5th, 6th, 7th and 8th anterior roots on the left and the entire cervical cord was decompressed. Three alternate rootlets of each root were cut. The minimal voltage necessary to produce peripheral muscular contractions was increased thereby 0.75 volt. The cervical cord was atrophied and compressed by scar. After considerable atonia in the arm during the first 10 postoperative days all voluntary motion reappeared, and the spasm was found to have been relieved about 50 per cent.

On June 19, 1951, the cervical scar was again excised, and the cord was re-exposed and rotated so that the right 5th, 6th, 7th and 8th anterior roots were in the field. Three rootlets

FIGURE 4. *Case 3: Two and a Half Months after Rootlet Section.*

Note absence of spasm of legs and feet and patient's ability to support part of his own weight.

of C_5 and C_6 respectively, four of C_7 and one of C_8 were cut. After the rootlet section had been completed it was found that the minimal current necessary to produce a peripheral motor response had been increased approximately 1.5 volts. After this operation there was virtually complete motor paralysis of the right arm and hand for about 2 weeks. Voluntary motion gradually increased, however, and in another two weeks had returned to its preoperative level. Simultaneously the spasm had been decreased about 75 per cent. It was now possible, for the first time, to use physiotherapy and active and passive muscle training with effect, and by the middle of September, 1951, he had already regained enough normal use of his right hand to begin feeding himself (Fig. 2). The left hand, however, because of contractures, deformities and an ankylosis of the elbow, together with the residual uncorrected spasm, is still of little practical use.

CASE 3. K. Z., a 2-year-old boy, was admitted to the Boston City Hospital on January 30, 1951. He was born at full term by instrumental delivery, his birth weight being 12 pounds. When he was 3 months old it was noted that his right side was paralyzed and his eyes crossed; his legs were spastic and held in a "scissors position." At the age of 8 months electrical stimulation of the paralytic limbs was started; he improved during the following year enough to

FIGURE 5. *Case 3: Four Months after Rootlet Section.*

raise his limbs slightly off the bed. He had never been able to talk clearly but could understand commands.

On admission to the hospital the patient was capable of understanding simple commands, but his spontaneous speech was limited to 2 or 3 words, and he cried easily. His gait was a spastic scissors type, with "ballet-dancer" station, in which only the tips of his toes carried his weight; he required full weight support to be able to do even this (Fig. 3). He showed jerky nystagmoid ocular movements in all directions, with a coarse nystagmus, and he was unable to hold his head up when he was held erect. There were no athetoid or myoclonic motions. The tone of the leg muscles was normal with the patient supine or prone, but a change to the erect position caused immediate rigidity and scissoring of both legs. There were bilateral extensor plantar responses and slightly more active tendon reflexes on the right. There was a central-type facial weakness. An electroencephalogram was noncontributory. The usual laboratory studies were all within normal limits. The intracranial pressure, as measured by lumbar puncture, was 110 mm. cerebrospinal fluid. The cerebrospinal-fluid

protein was 15 mg. per 100 cc. and the gold sol 0000000000. The blood and cerebrospinal-fluid Wassermann and Hinton tests were negative. Stereoscopic x-ray films of the skull were normal except for a bony asymmetry that increased the fronto-occipital diameter and decreased the biparietal diameter. A pneumoencephalogram showed a bilateral, symmetrical, nonobstructive type of ventricular enlargement, with the left ventricle slightly larger than the right. The subarachnoid air shadows were within normal limits.

After careful consideration of all the factors involved, a low dorsal and lumbar laminectomy was performed on February 8, 1951, in order to carry out a bilateral rootlet operation. Attempts to determine the minimal electrical current that would produce contractions in the legs failed for technical reasons. Three dentate ligaments were cut on each side and the cord was rotated as necessary. On the left the entire anterior root of L_1 was cut, as well as the top rootlet of D_{12}. After this, every other rootlet of the next 5 anterior roots and then 2 rootlets in succession were cut. The lowest uncut rootlet when stimulated caused contraction of the gastrocnemius muscle and plantar flexion of the toes on the left. On the right, alternate rootlets were cut as on the left, 7 being divided and 5 being left intact. No bladder response to electrical stimulation was obtained on either side. The wound, including the dura, was closed without drainage.

The next day the right leg was atonic and without voluntary motion. There was no scissoring. This atonia disappeared in 12 days and voluntary motion returned to the preoperative level or better, except for a residual right foot drop. Five days postoperatively the indwelling urinary catheter that had been inserted at operation was removed. Voiding took place as prior to operation. On May 18 a triple hemisection of the right Achilles tendon was performed, and the patient was returned on June 16, 1951, to the institution for the treatment of cerebral spastics at which he had previously been cared for (Fig. 4). He has been seen twice in the interval, the last visit being on September 11, 1951. At this time, about 7 months after his operation and with only 3 months of training, he had greatly improved. As regards self-care activities, he now feeds himself with a fork and spoon, uses both hands to string beads, drinks from a cup unaided, is able to button large buttons, helps to dress himself and is being successfully toilet trained. He talks almost volubly and understands requests. This latter, however, may be associated with an increase in his knowledge of English as opposed to Polish (the language spoken in his home). He walks actively in a walker and also without it with a minimum of support. He does not climb stairs. He wears no braces or splints. Now 3 years old, he holds his head up normally (Fig. 5). The physiotherapist believes that the patient has gained in 3 months what would have taken at least 2 years without the operation and considers that he is probably already able to do things that would otherwise have been permanently impossible for him.

Summary

A method of dealing with the disabling type of peripheral spasm seen in certain patients with cerebral and spinal injuries is presented.

It is based on effecting a reduction of the number of motor impulses passing peripherally to the spastic muscles by reducing the pathways carrying such impulses by one half or one third.

This is accomplished by dividing one half or one third of the appropriate motor rootlets.

The operation has been performed to date on 3 patients, 2 with cervical-cord injuries and 1 with a spastic diplegic type of birth injury.

All patients showed some improvement in six months or less. The spastic diplegic patient showed the greatest gain.

On theoretical grounds, and as the result of a rather extensive experience in treating detrusor and external urethral-sphincteric spasm, it appears that effective control of this type of spasm is best obtained by interfering with the motor rather than the sensory limb of the spinal sensorimotor reflex arc.

CLINICAL EVALUATION OF AUREOMYCIN AND CHLORAMPHENICOL IN HERPES ZOSTER*

EDWARD H. KASS, PH.D., M.D.,† ROBERT R. AYCOCK, M.D.,‡ AND MAXWELL FINLAND, M.D.§

BOSTON

FROM a previous study of 24 consecutive cases of herpes zoster treated with aureomycin[1] the impression was gained that this antibiotic favorably influenced the course of the cutaneous lesions. Although postherpetic pain was not prevented in patients whose treatment was begun more than two weeks after the first appearance of the lesions, such pain was infrequent in those whose treatment was begun early and maintained in adequate dosage. Similar favorable results from the use of either aureomycin[2-15] or chloramphenicol[15-21] in isolated cases or in small numbers of cases of herpes zoster have now been reported by many observers.

One report, however, stated that the course of the disease was not favorably affected in 4 patients with herpes zoster treated with chloramphenicol. Indeed, in one of these 4 patients the lesions of herpes zoster first appeared after seventy-two hours of treatment with chloramphenicol for a chronic pulmonary infection.[22] The appearance of herpes zoster during the course of aureomycin therapy for other infections has also been reported by two independent observers.[23, 24]

At the time when the initial series of aureomycin-treated cases was reported, the possibility was entertained that a viral infection was involved in which the two broad-spectrum antibiotics exerted different effects. A controlled study was therefore undertaken in which aureomycin and chloramphenicol were given alternately to patients with active herpes zoster as they presented themselves. After the first few patients had been treated under this plan, some patients were referred for therapy in whom the course of the lesions and pain appeared favorable when they were first seen, in spite of the fact that antibiotics had not been given to them previously. They were not included in the study, and although no antibiotic was prescribed for these patients their subsequent course was entirely uneventful. It then became imperative that a group of comparable patients treated without antibiotics be included in the study for better evaluation of the effects of the antibiotics on the course of the disease. The present report deals with a comparison of the results in 3 groups of cases, one treated with aureomycin, a second treated with chloramphenicol and a third in which antibiotics were withheld and the patients treated with a simple analgesic.

MATERIALS AND METHODS

Seventy-seven patients with herpes zoster were treated, but 5 of them did not return for follow-up and are therefore not discussed in this report. The remaining 72 patients were selected at random in the out-patient department, admitting floor or wards of the Boston City Hospital between September, 1949, and July, 1951; and all were seen again in July or August, 1951, for final follow-up study. Twenty-five patients were treated with aureomycin, 25 received chloramphenicol and 22 received an analgesic tablet containing 180 mg. of acetylsalicylic acid, 120 mg. of phenacetin and 60 mg. of caffeine phosphate (Empirin Compound). Only 13 were treated in the hospital wards — 5 with aureomycin, 2 with chloramphenicol and 6 with the analgesic.

When the patients were first seen they were instructed to use no local therapy and to take no medication other than that dispensed. In no case were sedatives or narcotics used during the week after the patient was first seen. The attempt was made to see each patient 2 or 3 times during each of the first two weeks and less frequently thereafter as indicated.

When the study was initially undertaken, alternate patients were given aureomycin and chloramphenicol. When it became evident that data on the natural course of herpes zoster were urgently required for comparison, a consecutive series of patients equal in number to the antibiotic-treated groups were treated with the analgesic tablets alone; thereafter, successive patients were treated with aureomycin, chloramphenicol or analgesic, in rotation. Each patient was told that he was receiving a new and expensive medicine that was usually effective in the treatment of herpes zoster and was then given the number of capsules or tablets needed until the next visit. The patient was requested to return all unused medication at the end of the week. Aureomycin and chloramphenicol were dispensed as 250-mg. capsules,¶ and the initial dose prescribed was 3 or 4 gm. per day orally in 4 divided doses; one dose was to be taken after each meal and the fourth before bedtime with some food. The daily dose was decreased to 2 gm. per day after improvement occurred or if unpleasant side-effects were noted. The analgesic was given as 1 tablet four times daily.

Nearly all the patients were seen by a single observer, who recorded his findings in detail at each

*From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

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†Instructor in medicine, Harvard Medical School; senior fellow in virus diseases, National Research Council; research fellow, Thorndike Memorial Laboratory.

‡Teaching fellow in medicine, Harvard Medical School; assistant resident, Second Medical Service, Boston City Hospital.

§Associate professor of medicine, Harvard Medical School; associate director, Thorndike Memorial Laboratory; chief, Fourth Medical Service, Boston City Hospital.

¶The aureomycin was provided by Lederle Laboratories, through the courtesy of Dr. Stanton M. Hardy; the chloramphenicol (Chloromycetin) was supplied by Parke Davis Company, through the kindness of Dr. E. A. Sharp.

visit. The patients were questioned about their symptoms and the lesions were examined. The final evaluation of the effect of treatment was based on analysis of the recorded data according to criteria that had been defined beforehand. The lesions were considered to have cleared when all the crusts had fallen off and there was no evidence of secondary infection. At this stage pink macules or maculopapular areas frequently remained; these cleared very slowly but were not considered part of the acute process. Pain was classified as "severe" in patients who complained of constant burning, itching or lancinating pains that interfered with sleep and normal daily functions; pain of lesser intensity was classed as "moderate" or "mild."

Table 1. *Distribution of 72 Patients with Herpes Zoster by Age and Sex.*

Age	Patients Treated with Aureomycin		Patients Treated with Chloramphenicol		Patients Treated with Analgesic		All Cases
yr.	male	female	male	female	male	female	
Less than 20	0	1	1	1	2	1	6
20–49	3	5	4	4	4	1	21
50–69	5	6	6	5	5	6	33
70 or over	4	1	4	0	1	2	12
Totals	12	13	15	10	12	10	72

Analysis of Cases

Age and Sex

Table 1 shows the distribution of patients by age and sex according to three plans of therapy. There were 39 males and 33 females, almost half of whom were between fifty and sixty-nine years of age.

Seasonal Incidence

There was no unusual prevalence of the disease in any one season.

Special Features

Some antecedent diseases and other relevant features are listed in Table 2. The patients with diabetes were all under treatment with protamine zinc insulin and were well controlled. The patients with pernicious anemia were regular attendants in the clinic; they were receiving injections of liver extract periodically and were in good hematologic remission. Except for 2 sisters who developed herpes zoster about a week apart, only 1 patient had had a known recent exposure to this disease. There were 3 patients, however, who gave a history of a previous attack of herpes zoster. These attacks had occurred ten, fifteen and twenty years previously and involved a site other than that involved during the present study.

Relation to Varicella

The relation between chicken pox and herpes zoster was difficult to evaluate. Many of the patients were unable to recall whether they had had chicken pox, and many of those who answered affirmatively or negatively used terms so vague that their reliability is questionable. One patient had been exposed to varicella one month prior to the appearance of herpes zoster, but exposure to this disease was specifically denied by 43 patients. A previous history of varicella was given by 12 and denied by 21 patients; the remaining patients were uncertain whether or not they had had the disease.

Table 2. *Antecedent Illnesses in 72 Cases of Herpes Zoster.*

Antecedent Illness	Therapeutic Group			
	Aureomycin	Chloramphenicol	Analgesic	All Cases
Diabetes mellitus	4	2	1	7
Pernicious anemia	1	0	1	2
Arthritis	1	1	0	2
Miscellaneous	1*	4†	4‡	9
Exposure to herpes zoster	1§	1§	1	3
Exposure to chicken pox	0	1	0	1
Previous history of herpes zoster	1	1	1	3

*Draining abscess of buttock.

†Rheumatic heart disease with auricular fibrillation, 1; recent coronary thrombosis, 1; recent trauma, 1; pregnancy, 8 months, 1.

‡Cardiac failure, 1; idiopathic epilepsy, 1; acute and chronic alcoholism, 1; morphine addiction, 1.

§Sister treated for herpes zoster within 1 week.

Distribution of Lesions

Table 3 shows the distribution of the lesions in each group. Involvement of the thoracic segments occurred in about two thirds of the patients. There

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was no relation between sex and the occurrence of lesions at any given site. Of the 7 patients with trigeminal-nerve distribution 5 had involvement of the ophthalmic branch.

Occurrence of Pain and Rash

There was a rough correlation between the severity of the pain and the extent of the skin lesions, but in certain cases an extensive, almost bullous outbreak was accompanied by rather mild hyperesthesia and burning. Conversely, small areas of involvement were at times associated with severe subjective symptoms. The duration of pain and lesions before the patient was first seen is shown in Table 4; an estimate of the severity of symptoms and lesions is given in Table 5. Signs and symptoms in the three groups were judged roughly comparable. Most of the patients were seen within four days of the onset of either the pain or the rash. In about two thirds of the cases treated with antibiotics and in half of those who received the analgesic the disease was considered severe at the time treatment was started.

Severe pain was more frequent in the older patients. Thus, only one third of the patients under fifty years of age had severe pains, whereas about two thirds of those in the older age groups complained of severe pain.

Dosage

Although the attempt was made to have the patient take 3 to 4 gm. daily of aureomycin or chloramphenicol for one week, these amounts were not always well tolerated on this schedule. The total dose and the duration of treatment with the antibiotics are given in Table 6. The total amount of chloramphenicol actually taken was greater than that of aureomycin, although both agents were given for about the same length of time. The difference is due to the fact that the chloramphenicol was better tolerated.

TABLE 3. *Distribution of Vesicles in 72 Cases of Herpes Zoster.*

NERVE SEGMENT INVOLVED	PATIENTS TREATED WITH AUREOMYCIN	PATIENTS TREATED WITH CHLORAMPHENICOL	PATIENTS TREATED WITH ANALGESIC	ALL CASES	
				no.	%
Trigeminal	1	3	3	7	10
Cervical	2	5	2	9	12
Cervical and upper thoracic	1	1	2	4	6
Thoracic	16	12	12	40	56
Thoracolumbar	1	1	1	3	4
Lumbar	3	2	1	6	8
Lumbosacral	1	1	1	3	4
Totals	25	25	22	72	100

RESULTS

Effect of Therapy on Duration of Lesions

Aureomycin or chloramphenicol did not hasten the healing of the lesions in the antibiotic-treated patients as compared with those in the patients treated with the analgesic. Lesions cleared within two weeks after treatment was begun in 85 per cent of all patients. The effect of treatment on healing of lesions is shown in Table 7. Results in the three groups were quite comparable. The apparently longer duration of the lesions after treatment with

TABLE 4. *Duration of Pain and Vesicles Prior to Treatment.*

DURATION	AUREOMYCIN		CHLORAMPHENICOL		ANALGESIC	
days	PAIN	VESICLES	PAIN	VESICLES	PAIN	VESICLES
2 or less	3	9	5	9	1	4
3–4	10	9	7	13	6	7
5–7	6	4	11	3	10	8
8–10	2	1	1	0	3	2
11–14	4	2	1	0	3	1
Average duration	5.7 days	4.3 days	5.0 days	3.0 days	5.4 days	4.4 days

TABLE 5. *Estimate of Severity of Herpes Zoster at Onset of Therapy.*

THERAPY	ESTIMATED SEVERITY	
	MILD OR MODERATE	SEVERE
Aureomycin	9	16
Chloramphenicol	8	17
Analgesic	11	11
All cases	28	44

chloramphenicol may be related to the fact that most of the patients receiving this drug were seen and treated earlier in the course of their disease than those in the other groups, as shown in Table 4.

New crops of vesicles appeared after the onset of treatment in 3 patients who received aureomycin, in 6 who were treated with chloramphenicol and in 2 who were given the analgesic tablets. These new lesions appeared in 3 patients from four to six days after chloramphenicol was started; in the remaining patients the new lesions appeared within the first two days of therapy.

TABLE 6. *Total Dosage and Duration of Antibiotic Therapy.*

Total Dose gm.	Aureomycin	Chloramphenicol	Total Number of Days	Aureomycin	Chloramphenicol
11–15	12	4	4 or less	3	2
16–20	6	3	5–7	12	15
21–25	5	14	8–10	9	6
26–30	1	2	11–14	1	1
31 or more	1	2	15 or more	0	1
Average	16.9 gm	23.6 gm.	Average	6.8 days	7.4 days

TABLE 7. *Effect of Therapy on Healing of Lesions.*

Period from Onset of Therapy to Healing of Lesions	Patients Treated with Aureomycin	Patients Treated with Chloramphenicol	Patients Treated with Analgesic
days			
4 or less	7	1	2
5–7	4	7	8
8–10	5	5	4
11–14	6	6	6
15 or more	3	6	2
Average number of days	9.0	11.8	10.3

Effect of Therapy on the Duration of Pain

The duration of pain was not shortened by antibiotic therapy. Complete relief of pain within four days after beginning treatment was noted by about one third of the patients and within seven days by half of the patients, as shown in Table 8.

The difficulties of judging therapeutic efficacy in herpes zoster were emphasized by the finding that in 37 of the 72 patients the pain was markedly improved within four days after therapy was begun and that in 48, or two thirds of the patients, the pain was greatly alleviated by the end of the first week of therapy. Post-herpetic neuralgia (pains of appreciable severity persisting for more than thirty days) occurred in 18 per cent in all cases and was distributed almost equally among each of the 3 groups.

That the initial severity of the symptoms was an important prognostic factor is indicated by the finding that 15, or 54 per cent, of the 28 patients with initially mild symptoms became symptom free within ninety-six hours after they were first seen. On the other hand, only 8, or 18 per cent, of 44 with initially severe pain were markedly improved within ninety-six hours after they were first seen. Likewise, of 23 patients who were completely relieved of pain within four days only 8, or 35 per cent, had severe pain initially, whereas 36, or 73 per cent, of 49 patients who had pain for longer periods after the onset of therapy had severe pain before treatment was started. The occurrence of post-herpetic neuralgia, however, did not seem to be related to the initial severity of pain; this sequel occurred in 4 (14 per cent) of the patients with initially mild pain and in 9 (20 per cent) with initially severe pain.

Estimate of Beneficial Effects of Therapy

A general estimate of the response to treatment was made in each case after all features were considered. The results are summarized in Table 9. There was no significant difference attributable to the type of therapy used. On the other hand, when the initial severity of the disease was considered, the

TABLE 8. *Effect of Therapy and of Initial Severity on Duration of Pain.*

Period from Start of Therapy to Complete Relief of Pain	Patients Treated with Aureomycin		Patients Treated with Chloramphenicol		Patients Treated with Analgesic	
	Mild or moderate pain	Severe pain	Mild or moderate pain	Severe pain	Mild or moderate pain	Severe pain
days						
0	0	0	0	0	1	0
1–2	2	1	1	1	4	0
3–4	3	1	1	3	3	2
5–7	1	3	2	3	1	3
8–30	1	8	2	8	2	2
More than 30	2	3	2	2	0	4
Totals	9	16	8	17	11	11

best results were achieved in those with initially mild pain; this was true regardless of the therapy used.

Since the possibility remained that the failure to demonstrate a beneficial action of the antibiotics was due to failure to institute treatment early in the disease, the data were re-examined after the exclusion of all patients in whom treatment was begun more than four days after the appearance of the first symptom. Among the 28 patients who were treated within four days of onset, 20 were considered to have had a good or excellent result.

TABLE 9. *Estimated Benefit from Therapy in Relation to Initial Severity and Early Treatment.*

THERAPY	INITIAL SEVERITY	ESTIMATED BENEFIT: EXCELLENT OR GOOD	ESTIMATED BENEFIT: EQUIVOCAL OR NONE
Aureomycin	Mild or moderate	7	2
	Severe	8	8
	Totals	15	10
Chloramphenicol	Mild or moderate	3	5
	Severe	8	9
	Totals	11	14
Analgesic	Mild or moderate	9	2
	Severe	4	7
	Totals	13	9
PATIENTS TREATED WITHIN FOUR DAYS OF ONSET*			
Aureomycin		8	5
Chloramphenicol		7	3
Analgesic		5	1

*Of pain or lesions, whichever occurred first.

Differences in the three groups are probably not significant.

Influence of Associated Diseases

The 2 patients with pernicious anemia had severe symptoms; the first, treated with aureomycin, developed post-herpetic neuralgia, whereas the second, who received Empirin Compound, did not. In addition to these 2 patients, another case of severe herpes zoster was reported to us; this occurred in a woman with pernicious anemia in whom aureomycin was ineffective and post-herpetic neuralgia resulted. These 3 patients with pernicious anemia were all in good hematologic remission. Five of the 7 patients with diabetes mellitus presented with severe pain; 4 of the 7 had poor results, and 2 developed post-herpetic neuralgia (1 treated with aureomycin and 1 with analgesic tablets). Other conditions listed in Table 2 did not seem to influence the course.

Side-Effects of Antibiotic Therapy

The occurrence of unpleasant side-reactions due to the antibiotics is listed in Table 10. Chloramphenicol produced slightly less reaction and was prescribed in larger total doses than aureomycin, but the difference was small. Sixteen of 25 aureomycin-treated patients and 12 of 25 chloramphenicol-treated patients experienced some untoward effect from ingestion of these antibiotics.

DISCUSSION

The data presented here do not support earlier impressions that aureomycin and chloramphenicol alter favorably the course of herpes zoster.[1] The findings are in agreement with those recently reported by Carter,[25] who treated 44 cases of herpes zoster and was unable to detect any advantage in the use of antibiotics. Carter treated 4 groups of 11 patients: one group received a placebo of glucose; the second, aureomycin orally, 2 gm. daily for six days; the third, aureomycin, 4 gm. daily for four days; and the fourth, chloramphenicol, 2 gm. daily for six days. Carter's data and those presented here indicate that in herpes zoster, contrary to common belief, most patients recover fairly promptly and without complications. The severe, painful sequelae that have been most difficult to manage were relatively infrequent in the present series; post-herpetic neuralgia occurred in but 18 per cent of the patients. Thus, the evaluation of a beneficial agent in herpes zoster requires observation of a sufficiently large number of treated and untreated patients to permit statistical comparison of both groups.

TABLE 10. *Side-Effects of Antibiotic Therapy.*

SIDE-EFFECTS	PLAN OF THERAPY: AUREOMYCIN	PLAN OF THERAPY: CHLORAMPHENICOL
Nausea and vomiting	5	1
Diarrhea	3	3
Nausea, vomiting and diarrhea	2	1
Epigastric distress	2	1
Anorexia and nausea	4	4
Sore mouth	0	3*
None	9	13

*One patient also had diarrhea and perianal pruritus.

Although antibiotics might benefit herpes zoster by reducing secondary infection, it was rare in this series, even among untreated patients. Despite frequent location of vesicles in areas where local trauma occurs readily and under circumstances that predispose to bacterial contamination, only 1 of 22 patients who did not receive an antibiotic developed clinical evidence of secondary infection. This patient had used various ointments before admission to the study group and had also developed dermatitis medicamentosa. It is possible that the mononuclear exudate in the vesicles is in some way concerned with the failure of bacterial invaders to cause more manifest secondary infection than was observed.

Limited data on patients with pernicious anemia and diabetes suggest a tendency to more severe symptoms and more persistent pain among patients with those disorders in which neuronal damage is common.

Conclusions

An analysis of observations made in 72 patients with herpes zoster reveals no measurable effect of the use of aureomycin or chloramphenicol as compared with the use of a simple analgesic.

The lesions of herpes zoster cleared within two weeks after their first appearance in more than three fourths of the patients and pain was completely relieved in less than two weeks from its onset in more than half the patients, irrespective of the type of therapy used.

Post-herpetic neuralgia (pain of more than one month's duration) occurred in only 18 per cent of the cases in this study.

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ACTIVATION OF LATENT HERPES SIMPLEX BY TRIGEMINAL SENSORY-ROOT SECTION*

Charles A. Carton, M.D.,† and Edwin D. Kilbourne, M.D.‡

NEW YORK CITY

IT IS now widely accepted that most adults are latently infected with the virus of herpes simplex.[1, 2] This latent infection may be activated by a large number of apparently dissimilar stimuli such as fever, exposure to sunlight, trauma and catamenia and may become manifest as vesicular lesions. The activating stimuli may produce such diverse and uncontrollable effects on the human organism, however, that the study of their relation to exacerbations of activity is difficult. The frequently made clinical observation that trigeminal sensory-root section for trigeminal neuralgia is often followed by facial herpes prompted the study of this phenomenon in some detail, because of the specific nature of the provoking stimulus. Furthermore, the availability of trigeminal-nerve tissue made possible a reinvestigation of the question originally raised by Goodpasture[3] of the existence of latent herpes simplex virus in the trigeminal nerve and Gasserian ganglion. Experiments with laboratory animals have demonstrated invasion of the central nervous system through the trigeminal nerve and ganglion,[4, 5] and pathological studies in man have revealed inflammatory changes in the Gasserian ganglion coincident with the presence of herpes labialis at death.[5, 6] Efforts to demonstrate herpes simplex virus in Gasserian-ganglion tissue have been unsuccessful,[7, 8] but virus has not been sought in nerve tissue from patients with active herpetic manifestations. Evidence for the herpetic etiology of the facial lesions that follow trigeminal sensory-root section has been tendered by Richter,[7] who recovered virus from 3 patients who developed labial vesicles postoperatively. Richter attributed the postoperative appearance of herpes to an alteration of the metabolic state of the skin that predisposed it to external invasion.

Cushing was perhaps the first to comment on the relation between operations on the trigeminal ganglion and the subsequent appearance of herpes facialis.[9-11] In a series of 20 ganglionectomies he observed 2 cases in which herpetic lesions occurred on the sixth and the seventh postoperative day respectively, both in association with herpes zoster of the sacral region. In one case the vesicles were on the upper lip and on the nasal ala of the unoperated side; in the other case, in which previous supraorbital and

*From the Service of Neurological Surgery, Neurological Institute, Presbyterian Hospital, and the Hospital of the Rockefeller Institute for Medical Research.

†Senior resident, Service of Neurological Surgery, Neurological Institute, Presbyterian Hospital.

‡Formerly, fellow, Rockefeller Institute for Medical Research; associate professor of medicine and director, Division of Infectious Diseases, Tulane University School of Medicine.

infraorbital neurectomies had been performed, the lesions were bilateral and occurred on the unoperated side of the nose, upper lip, cheek and angle of the jaw and on the operated side near the angle of the jaw outside the postoperative area of sensory loss. Cushing concluded from these observations "that the presence of the ganglion semilunare... is essential for the production of herpetic eruptions of this nature, since in both cases the cutaneous area rendered anesthetic by the extirpation remained free from vesiculation."[20] Careful review of the data in his second case reveals that there were lesions within the hypesthetic area along the ramus of the mandible on the operated side. He believed that "posterior root ganglion lesions were responsible for the common form of herpes about the lips and nose, as well as for zoster."[9]

The objectives of the present study were: to establish the herpetic etiology of the postoperative vesicular facial lesions that appear after trigeminal sensory-root section; to determine by antibody studies whether postoperative herpes simplex represents a primary or a recurrent infection; to attempt recovery of herpes simplex virus from specimens of trigeminal sensory root or Gasserian ganglion removed at operation; and to ascertain whether there is any correlation among the cut portion of the trigeminal sensory root, the area of the face denervated by operation and the location of the herpetic lesions.

Materials and Methods

Seventeen patients suffering from classical trigeminal neuralgia (tic douloureux) were studied during their hospitalization for selective section of the posterior root of the affected trigeminal nerve. This group was composed of 8 women and 9 men between forty-seven and seventy years of age. None had received nerve block with alcohol or procaine injections. Eight patients gave definite past histories of herpes labialis and 1 denied previous lesions; historical data relative to herpetic infection were not available on the remaining 8 patients. All operations were performed through the middle fossa, subtemporal, extradural route, sparing the motor root when possible; differential sections of the sensory root were performed when indicated. Sensory loss following operation (or additional sensory loss, if sensory defect was present preoperatively) was carefully plotted, as were any evidences of motor complications such as trigeminal-nerve or facial-nerve paralysis. Postoperative herpetic eruptions were studied with reference to time of appearance, location, duration and attendant constitutional symptoms. All patients were examined daily after operation for the appearance of herpetic lesions. As soon as vesicles were discovered, specimens of fluid were obtained on sterile swabs, which were immediately immersed in phosphate-buffered saline solution and frozen in an ethanol-CO_2 mixture prior to storage at −65°C. In patients whose antibody concentrations were studied, serum specimens were obtained prior to surgery and fourteen to twenty-one days subsequently. Specimens of sensory-root and ganglion tissue were quick-frozen in the operating room immediately after excision. These specimens were thawed and ground in a mortar directly prior to inoculation into animals. Vesicle fluid was inoculated intraperitoneally into newborn Swiss mice[12] after the addition of penicillin and streptomycin to the specimens. Estimation of neutralizing antibody concentration in serums and neutralization of newly isolated herpes strains with specific herpes antiserum were effected by methods described by Kilbourne and Horsfall.[12]

Experimental Results

In all but 1 patient, labial vesicles appeared forty-eight to ninety-six hours after operation. In 5 cases ulcerative lesions of the palate were observed as well. Lesions appeared on the side of the nerve-root section; they persisted for approximately five days and were not accompanied by any evidence of systemic infection. Although vesicles on the lips appeared most often at the mucocutaneous junction, they were also seen on the skin of the chin and cheek. Herpetic lesions of the eye or ear, including the tympanic membrane, were not observed. All palatal lesions were restricted to the denervated side, although bilateral lip lesions appeared in 1 patient. In this case the lesions on the side opposite the nerve section appeared last; these may have arisen by contiguity from the initially apparent lesions of the side operated on. Lesions were usually restricted to areas supplied by the sectioned portion of the trigeminal sensory root, although lesions did not always appear in denervated areas. An exception was Patient 11 (Table 1). Although nerve-root section in this patient was presumably restricted to third-division fibers, vesicles appeared in the dermatome of the second division. The possibility exists, however, that some second-division fibers were inadvertently severed. The correlation between trigeminal nerve-root section and the appearance of vesicles is shown in Table 1, which summarizes data relative to operative procedure, postoperative herpes and virus and antibody studies. In most cases the labial lesions were the most extensive and severe, constituting unusually acute attacks in the patients so afflicted. In 13 patients motor-root damage was evident in the immediate postoperative period. The appearance of herpes lesions in patients in whom motor function was preserved makes it unlikely that motor-nerve damage is related to their induction.

Herpes simplex virus was recovered after injection of newborn mice from lip vesicles in all cases in which specimens were obtained. The virus was isolated once also (from Patient 14) by chick-embryo and rabbit inoculation. Another time virus (from Patient 2) was recovered separately from both labial

and palatal lesions. All strains were neutralized by antiserum against known herpes simplex strain K as described by Kilbourne and Horsfall.[12, 13]

The inoculation of infant mice, chick embryos and rabbits with 20 per cent suspensions of ganglion tissue in 2 cases (Patients 2 and 5) failed to produce manifest disease in any of the three hosts, despite serial passage of mouse and chick-embryo materials.

geminal sensory-root section, with lesions strikingly restricted to the denervated areas of skin or mucosa. Herpes simplex virus was obtained from all lesions from which its recovery was attempted, but it could not be demonstrated in excised Gasserian-ganglion and sensory-root tissue. Evidence provided by clinical histories and antibody studies indicated that all 11 patients on whom such information was

TABLE 1. *Correlation Between Trigeminal Sensory-Root Section and Location of Herpes Simplex.*

Case No.	Age	Sex	Sensory-Root Fibers Sectioned*	Postoperative Herpes		Specimen Obtained from Lesions	Virus Recovery from Specimen	Preoperative Antibody†	Herpes History
				Skin Innervation of Herpetic Site	Location of Lesions				
	54	F	L‡-1, 2, 3	L-2, 3	L upper lip; L hard palate; R upper lip (later).	+	+	N. D.§	+
2	47	F	R‡-2, 3	R-2, 3	R upper and lower lips; R hard palate.	+	+	+	+
3	61	F	R-1, 2, 3	R-2, 3	R hard palate; R lower lip.	+	+	N. D.	+
4	58	M	R-2, 3	R-2	R upper lip	+	+	N. D.	+
5	70	M	L-1, 2, 3	L-2, 3	L upper and lower lips; L chin.	+	+	N. D.	+
6¶	62	F	R-1, 2, 3	No lesions	No lesions			+	0
7¶	61	M	R-1, 2, 3	R-2, 3	R upper and lower lips			N. D.	+
8	51	M	L-2, 3	L-2, 3	L upper and lower lips	+	+	N. D.	?
9	56	M	L-1, 2, 3	L-3	L lower lip			N. D.	+
10	50	F	L-1, 2, 3	L-3	L lower lip			N. D.	?
11	62	F	R-3	R-2	R upper lip; R hard palate.			N. D.	?
12	69	M	L-2, 3	L-2	L upper lip; L cheek.			N. D.	?
13	59	M	R-1, 2, 3	R-2, 3	R upper and lower lips; R palate.	+	+	N. D.	?
14	63	F	R-1, 2, 3	R-2	R upper lip; R hard palate.	+	+	+	+
15	67	M	R-1, 2, 3	R-3	R lower lip			+	?
16	69	F	R-1, 2, 3	R-2, 3	R upper and lower lips			N. D.	+
17	49	M	L-2, 3	L-2, 3	L upper and lower lips			N. D.	?

*Verified by postoperative sensory examination.
†Neutralizing antibody; 1:4 serum dilution neutralized 100 LD_{50} of herpes simplex virus.
‡L = left; R = right.
§N. D. = not determined.
¶Reoperation.

Labial lesions appeared postoperatively in these 2 patients.

Studies of antibody in four cases selected at random revealed significant concentrations of herpes neutralizing antibody in all prior to operation and to the appearance of herpetic lesions. It is of interest that antibody was likewise demonstrable in 1 subject (Patient 6) who did not develop clinical manifestations of postoperative herpes. In another patient, no change in antibody concentration was detected in serum obtained four days before and fifteen days after the development of labial and palatal lesions.

Discussion

Among these 17 patients clinical manifestations of herpes simplex occurred in all but 1 after trigeminal available had previously experienced clinical attacks of herpes simplex. The postoperative herpetic manifestations thus probably represent reactivation of previously existing latent infection rather than external invasion by herpes simplex virus, as was postulated by Richter.[7]

In human beings subjected to artificially induced fever, herpes simplex develops in a high proportion of cases, ranging from 46.2 to 70.7 per cent.[14, 15] In these patients lesions occurred chiefly within the sensory distribution of the trigeminal nerve but were characterized by their symmetry[14] and bilateral distribution. Furthermore, occasional onset of encephalitis noted after the artificial production of fever has suggested activation by fever of herpes simplex virus in other sites, as, for instance, within the central nervous system.[14] In this series the herpetic sequelae of posterior trigeminal-root

section were circumscribed and homolateral, appearing on the skin areas denervated by nerve section. The incidence of manifest herpes in this small series was higher (94 per cent) than that occasioned by the stimulus of artificial fever approaching a regular, predictable phenomenon.

A procedure for the predictable provocation of a latent infectious agent into clinical activity has considerable theoretical interest, particularly in view of the specific nature of the exciting stimulus. Although the stimulus of fever is attended by profound physiologic changes that might conceivably disturb humoral immune mechanisms, it seems unlikely that the effects of an operation for trigeminal sensory-root section would extend significantly beyond the innervated tissue. Thus, understanding of tissue-metabolism changes following sudden surgical denervation may yield insight into the mechanisms of virus activation and multiplication.

The preceding statements are based on the supposition that postoperative herpes represents the activation of virus *in situ* in previously invaded peripheral tissues by some "trigger" mechanism released by sensory-root section. Presently available evidence does not appear to support the original speculation of Goodpasture that virus latent in the Gasserian ganglion is activated to spread peripherally along the fifth-nerve fibers to the skin. Although all three trigeminal sensory-root divisions were sectioned in 10 patients of the present series who developed postoperative herpes, vesicles did not develop in all three of the denervated areas in a given case. Moreover, lesions were never observed in the distribution of the first division.[16] Although slit-lamp examination of the cornea admittedly might have revealed evidence of herpetic keratitis, the more easily detectable labial lesions often failed to appear in both second- and third-division areas after section of both divisions. It therefore appears unlikely that virus activated in the ganglion would selectively restrict its migration and infectivity to cells of only one or two of the three divisions. The sporadic appearance of lesions in the denervated areas and their frequent occurrence in the buccal regions known to be the site of primary infection are more easily explained as results of the activation of residual islands of latent virus in skin and mucosa.

Although herpes simplex virus has not been demonstrated in the Gasserian ganglion, disturbance of ganglion cells may be essential to the provocation of herpes, for it is notable that section of the sensory root near the pons through the posterior fossa produces a homolateral herpetic eruption in an estimated 10 to 15 per cent of cases,[17, 18] and peripheral alcohol and procaine injections are also infrequently followed by herpes.

Circumstances of the 1 case (Patient 6) in which herpes simplex was not observed postoperatively suggest possible mechanisms of virus activation. This patient had previously undergone a supposedly complete sensory-root section that had resulted in loss of pain and diminished sensation in areas supplied by the second and third divisions although some sensation was preserved in the first division. Reoperation with total sensory-root section was carried out in order to denervate the first division completely. The failure of the second operation to precipitate herpetic lesions may illustrate the dependence of virus activation on section of intact sensory fibers, as the fibers of the second and third divisions had already been cut. However, in the absence of adequate observations concerning the appearance of lesions after the *first* operation, this interpretation remains speculative. It is notable that Patient 7, also subjected to reoperation, developed labial vesicles after both operations, but pain fibers were intact prior to the second sensory-root section. Fuller explanation of the phenomenon of herpes simplex virus activation by trigeminal-root section must await further studies of patients and comparable laboratory experiments.

Summary

Herpes simplex occurred in 16 of 17 patients after trigeminal sensory-root section for trigeminal neuralgia.

The lesions were homolateral to the nerve sectioned and were usually within the distribution of the second or third division or of both. No vesicles developed in areas of skin innervated by the first division. No relation was observed between damage to the motor trigeminal root and the appearance of the herpetic lesions.

Herpes simplex virus was obtained from postoperative herpetic vesicles in each of 8 patients from whom its recovery was attempted.

Herpes simplex virus was not recovered from two specimens of Gasserian ganglion obtained at operation from patients who later developed herpetic vesicles.

Evidence provided by histories and antibody studies favors the hypothesis that herpes simplex infection occurring after trigeminal sensory-root section results from the provocation of latent herpes simplex virus. It is suggested that virus is activated *in situ* as the result of local changes in tissue metabolism secondary to interference with the sensory innervation of latently infected tissues.

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JAUNDICE OF HEPATIC ORIGIN DURING THE COURSE OF METHYL-TESTOSTERONE THERAPY*

IRVING B. BRICK, M.D.,† AND LAURENCE H. KYLE, M.D.†

WASHINGTON, D. C.

THE occurrence of jaundice during methyltestosterone therapy was recently reported by Kinsell[1] and Werner, Hanger and Kritzler.[2] In view of the apparent rarity of this toxic effect of a commonly used drug, as reflected by the sparsity of cases reported in the literature, and of the distinctive features of this type of liver disease, we are reporting two cases of jaundice that occurred during the sublingual use of methyl testosterone. Furthermore, widespread knowledge of this possibility may stimulate others to report and may serve as a warning that methyl-testosterone administration should be considered in the differential diagnosis of jaundice — especially in view of the unique laboratory findings appearing in these cases.

CASE REPORTS

CASE 1. (G.U.H. 32365). A 44-year-old lawyer entered the hospital on May 8, 1950, because of jaundice. The patient had been in his usual state of health until 10 days prior to admission, when weakness, loss of appetite, easy fatigability and nausea after meals were noted. During the next 5 days these symptoms continued, and he vomited once. Five days before he was hospitalized the patient's scleras were observed to be yellow, and he noted darker urine and lighter stools than usual. The yellow discoloration was next noted in his skin. Because of continuation of all symptoms he sought medical care.

For many years this patient had seen physicians for various complaints: severe headaches, vague gastrointestinal complaints such as gas, belching and bloating, aches in the arms, aches in the chest, lack of libido and constipation. These complaints usually occurred separately. Several diagnostic studies had revealed only a small hiatus hernia. Various functional diagnoses had been made.

Because of complaints of easy fatigability, loss of libido and potency and occasional hot flashes, testosterone propionate was administered intramuscularly for 8 months by a nurse who sterilized the needle and syringe before each injection. The dosage was 75 mg. weekly for 3 months followed by 25 mg. weekly for 5 months. As the patient improved on this regimen, he was transferred to sublingually given methyl testosterone, 30 mg. daily, and had been taking this for 7 weeks immediately prior to the onset of the present illness. No blood or plasma transfusions had been given.

Physical examination of the patient on admission revealed a deeply jaundiced apathetic man who appeared very ill. The liver edge was felt 3 cm. below the right costal margin in the midclavicular line. Tenderness in the right upper quadrant was elicited only by striking the right lower ribs. Small internal hemorrhoids were present.

Examination of the blood revealed a hemoglobin of 14 gm., a hematocrit of 46 vol. per cent, a white-cell count of 7200, with a normal differential, and a total eosinophil count of 127. A blood test for syphilis was negative. The icteric index on admission was above 100 units. Pertinent laboratory and liver-function tests are shown in Table 1. Daily urine-urobilinogen determinations (2-hour specimen) were negative until the 12th hospital day, when the specimen showed 3.12 Ehrlich units. Thereafter the determinations were within normal limits. Qualitative fecal urobilinogen determinations were negative until the 10th hospital day and thereafter were positive.

The patient was placed on a high-protein, high-carbohydrate, moderate-fat diet and on complete bed rest except for bathroom privileges. On the 5th and 6th hospital days exces-

TABLE 1. *Admission Laboratory Findings in Two Cases of Hepatic Jaundice.*

CASE	CEPHALIN FLOCCULATION	THYMOL TURBIDITY	SERUM ALKALINE PHOSPHATASE	SERUM PROTEIN			SERUM CHOLESTEROL				PROTHROMBIN
				TOTAL	ALBUMIN	GLOBULIN	TOTAL	FREE	ESTER	RATIO F/T	
		units	*Bodansky units*	*gm./100 cc.*	*gm./100 cc.*	*gm./100 cc.*	*mg./100 cc.*	*mg./100 cc.*	*mg./100 cc.*		*% of control*
1	++	5	17.2	5.8	3.9	1.9	155	92	63	0.59	38
2	0	2.5	22.2	—	—	—	252	146	106	0.58	85

*From the Departments of Medicine, Georgetown University Hospital and Georgetown University School of Medicine.

†Assistant professor of medicine, Georgetown University School of Medicine.

sive bleeding was noted with bowel passage. Since the prothrombin time was 20.9 seconds or 38 per cent of the control, 1 gm. of vitamin K oxide was administered intramuscularly. Subsequent prothrombin determinations indicated a gradual return to normal. After the first week the patient's appetite returned, and symptoms had largely disappeared by the second week. For the first 2 weeks of hospitalization a moderate degree of pruritus was noted. The jaundice faded slowly; by the middle of the 6th hospital week the total serum bilirubin was 0.86 mg. per 100 cc. and the icteric index was 9 units. A bromsulfalein test (5 mg. per kg. of body weight) showed 2 per cent retention at 45 minutes. The liver edge could not be felt by the 5th week of hospitalization. The patient was discharged on June 20, 1950.

The patient has been seen several times since discharge and has returned to his previous activities. Eight months after discharge there had been no return of hepatic symptoms and physical examination was not remarkable.

Case 2. (G.U.H. 36867). A 63-year-old man was admitted to the hospital on September 5, 1950. He had been in his usual state of health until 3 weeks prior to admission, when he noted progressive darkening of his urine, which continued until admission. Ten days prior to admission he sustained a sunburn and had a febrile reaction for 48 hours. Seven days before admission yellowing of scleras and skin, the onset of generalized pruritus, nausea, lack of appetite and light-colored stools were noted. The symptoms persisted until admission.

The patient, a veterinarian, was employed as an inspector of meat and had not worked with animals for several years. Three years previously he had sought medical care because of intolerance of cold, fatigue, loss of libido and potency, decrease in pubic hair and anorexia. Treatment with desiccated thyroid had resulted in no obvious improvement. One year previously he had noted a severe headache followed by vomiting and soon thereafter by unconsciousness. Hospital study disclosed subarachnoid hemorrhage and an aneurysm of the right middle-cerebral artery. He was also found to have hypopituitarism, the most prominent target-gland failure being found in the thyroid gland and the gonads. The administration of testosterone propionate resulted in marked clinical improvement, and the addition of small amounts of thyroid aided the response to treatment. He continued to use the testosterone propionate, 25 mg. thrice weekly for 8 months. These injections were given by his wife, who used the same syringe and needles. This equipment was purchased by the patient and was used by no one else. He received no injections of any other type during this period. During the 4 months prior to the present admission, androgen therapy was given sublingually in the form of methyl testosterone, 30 to 40 mg. daily. His general health had been good except for intolerance to cabbage and occasional belching after meals. He had lost about 15 pounds in the 3 to 4 weeks preceding hospitalization.

Physical examination was not remarkable except for intense generalized jaundice. The liver was not palpable and there was no tenderness or spasm in the right upper abdomen.

Examination of the blood count showed a hemoglobin of 14 gm., a hematocrit of 42 vol. per cent and a white-cell count of 6050, with 69 per cent lymphocytes, 2 per cent monocytes and 28 per cent polymorphonuclear leukocytes. The icteric index was 75 units, and the serum bilirubin was 6.8 mg. per 100 cc. The total eosinophil count was 116. Other laboratory and liver-function tests are listed in Table 1. Qualitative urine-urobilinogen tests were essentially negative until the 12th hospital day, after which time positive tests were reported.

Pruritus was the most troublesome symptom. A film of the abdomen showed two round areas of calcification in the region of the gall bladder that were interpreted as gallstones. Barium examination of the upper gastrointestinal tract was normal except for a slight irregularity in the descending loop of the duodenum. In view of the findings, the jaundice was thought possibly due to an extrahepatic obstructing lesion, either gallstones or a neoplasm. A surgical consultant noted a palpable gall bladder, a finding not affirmed by other observers. An exploratory laparotomy was performed after the patient was prepared for surgery with adrenocorticotrophic hormone.

Thorough examination of the pancreas, duodenum, common duct and gall bladder revealed stones in the gall bladder, but the common duct was normal and there was no evidence of extrahepatic obstruction. The pancreas and duodenum were also normal. A cholecystectomy and liver biopsy were carried out. The patient's postoperative course was complicated only by a toxic psychosis, but he recovered satisfactorily and his jaundice began to fade. He was discharged on October 21, 1950, and has been followed for 4 months. His condition is good, and there has been no recurrence of symptoms.

Microscopical examination of the liver-biopsy specimen showed a slight scattering of inflammatory round cells within the sinusoids and a few small focal aggregates of similar cells. Bile capillaries distended with bile pigment were noted; these appeared to be most numerous in the central areas of the lobules. Some of the Kupffer cells in these areas also contained bile pigment. The portal canals appeared essentially unaltered. The parenchymal cells manifested moderate nuclear irregularity, and a few binucleated forms were observed. These changes were interpreted as indicating liver-cell damage and repair of moderate degree. The cause of the bile stasis was not recognized.

Jaundice appeared in both these cases during the administration of the usual therapeutic dosage of methyl testosterone for seven weeks and four months, respectively. The jaundice was severe and rather prolonged. Fever and chills were notably absent in the prodromal period. The laboratory findings of normal flocculation tests and elevated alkaline phosphatase were highly suggestive of obstructive jaundice. In both cases there was diminution of the serum cholesterol-ester fraction. The prolonged absence of urobilinogen in the urine also indicated an obstructive phenomenon. Although gallstones were found at operation in Case 2, no extrahepatic obstructive element was found as a cause of the deep and prolonged jaundice, which gradually subsided, its course apparently unaffected by the operation. The histologic change in the liver in the second case was certainly not that found in the usual case of infectious hepatitis, as it did not show the characteristic widespread inflammatory reaction and parenchymal cell changes.

Discussion

Kinsell,[1] in a report of the treatment of 2 patients with chronic viral liver damage, reported that the protein balance was improved by the administration of testosterone. Without presenting any data on individual cases, the author commented that methyl testosterone had apparently resulted in jaundice in some patients. This had not been reported with the use of free testosterone or testosterone propionate. Kinsell postulated that since methyl testosterone causes profound creatine formation and excretion this process may occur at the expense of choline, with resulting decrease in phospholipid formation. Consequently, the use of methyl testosterone was believed contraindicated in patients with liver disease.

In a later communication,[3] Kinsell stated that 4 patients had shown jaundice during methyl-testosterone administration. The idea that the major loss of creatine, possibly resulting in a depletion of labile methyl groups, would lead to fatty infiltration of the liver with liver damage was not verified, as a liver biopsy taken in one case showed no fatty

infiltration. Although the patient was intensely jaundiced when the biopsy was taken, the liver cells did not appear abnormal. Incidentally, fatty infiltration has not been notable in any of the other liver biopsies reported.

Werner, Hanger and Kritzler,[2] in the first full report on this condition, described the clinical course of 7 patients who developed jaundice during methyl-testosterone therapy. Six of the patients received methyl testosterone orally for from eight days to four and one-half months in dosages ranging from 20 to 80 mg. daily. Another patient took 20 mg. of methyl testosterone daily sublingually for four and one-half months. No history of exposure to hepatotoxic agents or blood or plasma transfusions was given. The jaundice was intense and protracted in all cases. Recovery was apparently complete in all, no residual liver damage being noted in 2 cases available for long-term study. The laboratory findings were characterized by negative cephalin-flocculation and thymol-turbidity tests, moderate elevation of the serum alkaline phosphatase and a reduced serum cholesterol-ester fraction. The serum albumin and globulin determinations were normal, as were the sedimentation rates, serologic tests for syphilis and complete blood counts. In 2 cases 3 liver biopsies were taken in the course of the disease. The histologic lesion found was stasis of bile, with plugging of bile canaliculi in the central zones of the liver lobules and mild hepatic cell damage in these areas. There was no evidence of obstruction of the biliary system distal to the central zones.

Brief mention is made of a patient with jaundice and liver disease due to methyl-testosterone therapy who was treated with adrenocorticotrophic hormone by Thorn and his associates,[4] without sustained improvement in liver function. With the 2 cases presented in this paper, a total of 14 cases of jaundice during methyl-testosterone administration have now been reported. Liver biopsies in 4 patients of this group have uniformly shown only minimal liver-cell damage despite intense and protracted jaundice. In the liver biopsies of Werner, Hanger and Kritzler[2] and in our biopsy, bile plugs in the center of the lobules, with little demonstrable injury in the parenchymal cells or the portal triads, were noted. These histologic findings seem distinctive; together with the laboratory findings, which are essentially similar in our cases to those reported by Werner, Hanger and Kritzler,[2] they suggest a cholangitic or cholangiolitic variety of hepatitis. However, the latter authors comment on the characteristic histologic features of this entity, which distinguish it from the intrahepatic cholangiolitic obstructive jaundice that follows use of arsphenamine and other drugs. In the present cases the obstructive element is not explained by the histologic findings. Werner, Hanger and Kritzler[2] postulate that injury to the hepatic cells by methyl testosterone may lead to a disturbance of the normal hydration of the bile, which becomes too viscous to flow through the intralobular duct system.

These authors also point out that in these cases methyl testosterone is only indirectly indicated as the causative factor. Although similar chemical features may be found in rare cases of infectious hepatitis, the histologic findings definitely eliminate that diagnosis. A drug allergy or idiosyncrasy might be assumed, but this view must be accepted with caution, since in 2 of the 7 cases of Werner, Hanger and Kritzler[2] administration of methyl testosterone after recovery from jaundice failed to cause a recurrence of jaundice or of any liver impairment. One of the patients has taken the drug for four years since his recovery without deleterious effect. Pelner and Waldman[5] mention the use of methyl testosterone in the treatment of migraine in a discussion of "occupying" or "engaging" one or more of the liver functions as a new concept in therapy. Thus, they believe that methyl testosterone, in view of the excess excretion of creatine that occurs, causes a diminution of liver function, with jaundice, by competitive inhibition with dietary choline. However, the absence of fatty infiltration in the histologic studies tends to militate against this explanation of the effect of methyl testosterone on the liver. It is obvious that the mechanism of causation is not understood at present.

As pointed out previously, free testosterone and testosterone propionate have not been indicted as causes of jaundice. Only the methylated product has been implicated. Another methylated compound recently used is methyl thiouracil, for the treatment of thyrotoxicosis. It was thought advantageous to determine the incidence of jaundice with the use of this drug. It is well known that thiouracil and propylthiouracil have caused jaundice in a few cases, but this has been a minor problem in comparison with the occurrence of leukopenia. McCullagh and Sirridge,[6] in treating 100 patients with 200 to 300 mg. of methyl thiouracil daily, noted toxic effects in 5 patients, but it was necessary to discontinue therapy in only 1 case. Jaundice and liver impairment were not among the toxic effects listed. Thompson[7] collected data on 1300 cases treated with methyl thiouracil, with emphasis on the toxic reactions. The occurrence of jaundice was not mentioned; hence one can assume that jaundice occurs no more frequently during the administration of methyl thiouracil than with thiouracil or propylthiouracil.

It is therefore evident that the presence of the methyl group *per se* does not explain the causation of jaundice, since methylated thiouracil has not notably resulted in its occurrence. Furthermore, it is apparent that although methyl testosterone is a widely used preparation cases of jaundice are few, indicating the infrequency of this reaction. General

awareness of the possibility of jaundice during administration of this drug may bring to light more cases previously diagnosed as infectious hepatitis or subjected to exploratory surgery, as in one of our cases, since the picture may simulate obstructive jaundice. Although one cannot dogmatically state that these conditions are caused solely by methyl testosterone, the uniform characteristics of the course and the unique chemical and histologic findings tend to indicate that there is a significant cause-and-effect sequence.

Summary

Two cases of jaundice occurring during sublingual administration of methyl testosterone are reported. This brings the total number of such cases to 14.

The distinctive clinical course and unique laboratory findings are described.

Histologic study of liver-biopsy material reveals bile stasis in the central zones and minimal liver-cell abnormalities despite deep jaundice.

The mechanism of causation of this entity is not known.

Administration of methyl testosterone should be regarded as a possible etiologic factor in cases of jaundice.

Addendum

Since this paper was written, another case in this category has been encountered.

G.U.H. 36316 was a 36-year-old man who was admitted on November 26, 1951, because of malaise, anorexia, ease of fatigability and jaundice of 3 weeks' duration. There was also severe generalized pruritus. The urine was dark and the stools very light. On physical examination the patient was deeply jaundiced and the liver edge was palpated 2 cm. below the right costal margin in the right midclavicular line. The spleen was not felt. The serum bilirubin was 21.8 mg. per 100 cc. with 13.3 mg. in 1 minute direct. The alkaline phosphatase was 9.9 Bodansky units and the cephalin flocculation was negative in 48 hours; the thymol turbidity was 8.0 Maclagen units and the cholesterol 202 mg. per 100 cc. The serum albumin was 4.0 gm. and the globulin 3.6 gm. per 100 cc. Slight amounts of urine and fecal urobilinogen were present. Although the impression on admission was that of obstructive jaundice, surgery was delayed for further study. One of the authors saw this patient in consultation and elicited a history of previous medication for incomplete erection. It was ascertained from his private physician that the patient had taken methyl testosterone orally from August 15 to November 3, 1951, in a dosage of 20 mg. daily. A liver biopsy revealed findings similar to the histologic picture already described. The jaundice gradually diminished, and by January 9, 1952, only very slight scleral icterus remained. His general condition was good.

This is another case in which surgery was contemplated until the history of methyl testosterone medication was obtained. It seems obvious that in all cases of jaundice, inquiry concerning the previous use of methyl testosterone might be of value.

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MEDICAL PROGRESS

HORMONAL TREATMENT OF CANCER (Concluded)*

IRA T. NATHANSON, M.D.,* AND RITA M. KELLEY, M.D.†

BOSTON AND WALPOLE, MASSACHUSETTS

CARCINOMA OF THE PROSTATE GLAND

The treatment of cancer of the prostate gland by attacking the endocrine balance of the patient rests on firmer physiologic grounds, is better understood and yields more predictable results than the hormonal treatment of mammary carcinoma. The past six years have permitted a relatively long-term follow-up of the first patients treated by these methods, as well as an opportunity to study large series of cases. These observations have contributed much to the establishment of a rational basis for the palliative treatment of advanced prostatic cancer.[4-9, 125-160] The concepts are based primarily on the fundamental work of Huggins, who demonstrated stimulating effects of androgens and inhibiting effects of estrogens on physiologic mechanisms in the prostate gland,[161-164] and on the observations of the Gutmans[165] on acid phosphatase in relation to normal and neoplastic processes in the prostate gland. From these studies it was soon recognized that prostatic cancer, unlike many other types of neoplasms, frequently resembled normal prostatic epithelium in its capacity for responding to steroid hormones and for elaborating acid phosphatase. Since it was shown that androgens stimulate acid phosphatase and that castration or estrogens depress the enzyme in prostatic cancer, clinical trials to eliminate androgenic activity were strongly indicated. The effects of these trials are now well established and will be discussed.

Clinical Response

There are two methods of providing antiandrogenic therapy. One is surgical castration. (Castration by radiation in the male is not effective because of relative radioresistance of the Leydig cells.) The other is estrogen administration. Striking initial effects are observed in between 70 and 80 per cent of cases with advanced primary and metastatic disease. The clinical response to the two methods is usually identical qualitatively; the main difference lies in the rate of response. Improvement after castration is usually dramatic and essentially immediate, whereas estrogen therapy is usually slower but equally satisfactory. The earliest signs of a favorable effect may appear within a few days after castration or several weeks after the institution of estrogen therapy. The initial effects are usually relief of pain, increase in appetite, improvement in urination, cessation of hematuria and weight gain. Subsequently there is gross evidence of regression of the primary tumor and soft-tissue metastases. Objective osseous changes detectable by x-ray occur later. Radical surgery of the prostate gland to relieve obstructive symptoms may be necessary, but sufficient shrinkage of the primary tumor may obviate the need of this. Recurrence of obstructive symptoms in favorable cases is unusual. The local lesion may regress to such an extent that it is no longer discernible on rectal examination. It is interesting that the primary lesion may remain in a state of complete regression even though metastases eventually recur and progress rapidly. Occasionally the primary tumor does not respond despite an otherwise favorable result. Many patients are able to return to their usual duties, completely symptom free, in a few weeks to a few months after treatment is begun.

Chemical Changes

Clinical improvement in most cases is paralleled by chemical shifts toward more normal values. As stated, prostatic cancer cells as well as normal prostatic cells liberate acid phosphatase. The serum acid-phosphatase levels may become elevated when the primary disease has extended beyond its capsule or has metastasized, especially to bone. This elevation is considered diagnostic of prostatic carcinoma. If the disease is entirely confined to the prostate gland there is no elevation of serum acid phosphatase, but normal levels are often encountered with extensive disease. It is believed by some that a normal acid phosphatase in the presence of extensive disease indicates the presence of tumor cells that do not behave like normal prostatic epithelium and hence do not produce acid phosphatase. Thus it has been predicated that tumors producing increased acid phosphatase are most likely to respond to therapy. The figures of Nesbit and Baum,[166] however, show that this is not always the case, for they describe a 60 per cent response to estrogens in the presence of bony metastases and normal acid phosphatase. In cases with an elevated phosphatase, castration produces a sharp drop within twenty-four to forty-eight hours; a similar but slower decline occurs under estrogen therapy. Twenty per cent of patients show no drop in acid

*From the Medical Laboratories, Collis P. Huntington Memorial Hospital (Harvard University), the Tumor Clinic, Massachusetts General Hospital, and Pondville Hospital (Massachusetts Department of Public Health), Walpole, Massachusetts.

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†Associate clinical professor of surgery, Harvard Medical School; associate visiting surgeon, Massachusetts General Hospital; surgeon, Pondville Hospital.

‡Public Health Service Research Fellow of the National Cancer Institute.

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phosphatase and no clinical improvement.[134] Failure of the acid phosphatase to decline is therefore a bad prognostic sign. A rise in acid phosphatase after an initial fall usually signals reactivation. Once having fallen in response to therapy, however, the acid phosphatase may not rise again with recurrence of disease; this perhaps signifies a change in the character of the cancer cell. Persistence of normal values, therefore, does not necessarily mean that the disease remains in abeyance.

The alkaline phosphatase is also elevated in 90 per cent of cases with osseous lesions because the bone lesions are osteoblastic.[141] According to Dean,[141] the amount of alkaline phosphatase so accurately represents the reaction of bone to invasion by the carcinoma that its quantitative assay gives reliable clinical information concerning the status of the patient. The alkaline phosphatase in favorable cases may rise after castration or estrogenic therapy as a result of stimulation of osteogenesis. It may then fall to normal if clinical improvement persists, as osteogenesis decelerates and bone lesions become inactive. If there is no response, the alkaline phosphatase remains elevated. When estrogens are used, only one third of the cases show an increase in this value soon after the beginning of therapy and the decline to normal is more gradual than after castration.[141] In the remaining patients who respond, there is no initial rise in alkaline phosphatase but a steady decline from pretreatment levels.

Estrogen Preparations and Dosage

Stilbestrol has been the estrogenic preparation most widely used in the antiandrogenic therapy of prostatic cancer, although equivalent doses of other synthetic and natural estrogens have been utilized as successfully. There is considerably more disagreement about optimal dosage here than in the treatment of female breast carcinoma with estrogens. Agreement is almost universal, however, that once estrogen therapy is initiated it should be continued for the rest of the patient's life. Some investigators, particularly those who made the early studies, report satisfactory results with doses of stilbestrol of ¼ to 3 mg. daily,[6, 126, 130, 150] especially in relatively asymptomatic patients with advanced disease. Later reports, however, cite higher amounts,[134, 147, 148, 152, 167] beginning with 10 to 15 mg. and reducing to a maintenance dosage of 1 to 5 mg. daily if the acid phosphatase is reduced and remains at an essentially constant level. Huggins[136] and Fergusson[149] prefer to maintain a dose level of 10 to 15 mg. indefinitely. In occasional patients developing sudden recrudescence, increasing the dose to 60 to 300 mg. may effect a remission.[149, 168]

Side-Effects

The side-effects of castration or estrogen administration in the male include loss of sexual power, shrinkage of the penis, excessive weight gain, often in feminine distribution, and change in facies. Painful enlargement of the male breast is common with estrogen treatment but does not occur after orchiectomy. Of interest is remission of the breast signs and symptoms in some patients even though therapy is continued. Nausea and anorexia may occur during the initial phase of estrogen administration, but in most cases these disappear as treatment proceeds or the dose is adjusted. Rarely, estrogens must be discontinued because of intolerable side-effects.

Duration of Response

The duration of the favorable response to castration or to estrogen therapy in advanced carcinoma of the prostate gland may be a few months to many years. It is difficult to calculate survival time from the literature because of lack of uniformity in the reports and also because some patients with inoperable prostatic cancer live comfortably for many years without treatment. Most cases of prostatic cancer occur in an age group in which the death rate is high because of other factors. There is no question of the palliative effects of this mode of therapy on patients with severe symptoms, but debate arises concerning whether the over-all survival time is lengthened by these measures. Herger and Sauer[130] express doubt that the course of the disease is influenced by treatment in many cases. Most authors agree, however, that there is a definite trend toward increased survival.[125, 129, 134, 136, 139, 143, 152, 153, 155, 159] The recent analysis by Nesbit and Baum[157] of pooled data on 1818 cases presents statistical evidence that life is prolonged. The over-all survival is greatest during the first twenty-four to forty-eight months with endocrine modification therapy.[138] The majority of patients in most series have relapsed within two and one-half years from the onset of treatment. Resorting to castration after failure of estrogen therapy occasionally produces further respite, but the reverse procedure of using hormones for reactivation following castration is seldom efficacious.

Choice of Time and Method of Therapy

There are two major points of debate in the application of antiandrogenic measures in prostatic cancer. They are the optimal time for initiating treatment and the choice between surgical and medical methods. The impressive results so far discussed have been observed mostly in patients with advanced, symptomatic metastatic disease, and many investigators would limit this form of therapy to this type of patient.[125, 127, 132, 136, 141, 144] This decision is based on the prolonged freedom from symptoms that these patients may enjoy without specific therapy in spite of advancing disease and on the fact that castration and estrogen therapy do not permanently retard the growth of the primary tumor or prevent the eventual occurrence or progression of

metastases. The proponents of this plan believe that if therapy is initiated before symptoms become marked patients might be deprived of significant clinical benefit. This is predicated on the probabilities that a receptive tumor will respond regardless of the stage of the disease and that the effects of hormonal alteration are self-limited regardless of when it is initiated.[3] There is a considerable group, however, who believe that for maximum response therapy should be initiated as soon as the diagnosis of carcinoma of the prostate is made, whether or not metastases are present.[126, 128, 139, 142, 149, 151, 154, 160, 169] Some investigators[149, 154] advocate the use of estrogens immediately after primary radical surgery to minimize potential metastatic activity, reserving castration until symptoms are pronounced. Harrison[160] advocates both castration and estrogen therapy at the time diagnosis is made and radical surgery undertaken. It is still too early to judge whether prophylactic antiandrogenic therapy will show a significant delay in or avoidance of the appearance of metastases.

The present trend among those physicians who do not initiate treatment until symptoms appear is toward the use of estrogens, unless severe pain, developing cachexia or progressive obstructive symptoms due to a rapidly enlarging primary lesion make the usually more rapid response to castration imperative. Deming[142] is of the opinion that estrogen therapy is more physiologic than castration. He believes that if the testes are left in place there is less stimulus to the adrenal glands to produce excessive androgen. Others[144, 150] share his belief in the merits of estrogen alone. Huggins favors orchiectomy as the superior mode of therapy, contending that the inhibition of androgens by estrogens is not complete and that estrogens must be given for prolonged periods and may be poorly tolerated or may even be potentially carcinogenic.[137] It has become routine in some clinics to use the two methods in conjunction rather than singly or in succession. Estrogen therapy is initiated as soon as castration has been accomplished, with no delay for observing the effects of castration alone.[126, 132, 160, 169] The pooled data of Nesbit and Baum[157] suggest that for cases without metastases combined therapy is most effective whereas in those with metastases orchiectomy is significantly more efficacious than stilbestrol therapy. They also believe that maximum benefit is achieved when therapy is instituted as soon as the diagnosis is established.

From the long-term follow-up of this aggregation of patients with different forms of treatment instituted at various phases of their disease, a pattern of response may eventually emerge that will serve as a more definitive guide in the choice of therapy. We cannot expect this for some years, but it is noteworthy that with any plan of hormonal therapy the over-all results are not notably different. This suggests to the authors that the biologic characteristics of the tumors are the primary factors in determining response and may account in part for the divergence of opinions.

Our discussion so far has assumed that patients selected for androgen control therapy are beyond the reach of radical surgery because of the extent of their disease — and that such treatment is purely palliative. The possibility of utilizing hormonal therapy as an adjunct in rendering localized but advanced prostatic cancer susceptible to attack by radical surgical procedures with the hope of cure is under investigation.[140, 153, 160, 168, 170] Gutierrez[168] considers that the most important use of estrogens or castration lies in their potentialities for converting initially inoperable cases into cases suitable for radical surgery. He believes it is important to distinguish between adenocarcinoma and scirrhous carcinoma in choosing patients for therapy, as only the former appear to be responsive to estrogens. The latter, however, are quite rare. He recommends that all patients with infiltrating adenocarcinoma rendering surgery impractical be given stilbestrol (1.5 to 3.0 mg.) for two months and then be subjected to radical perineal prostatectomy if the lesion is responsive. He contends that by such treatment the percentage of operable cases may be increased from 10 to 80 per cent. Harrison[160] believes that about one month of preoperative estrogen therapy is sufficient preparation. We believe that an optimum time for a radical surgical attack on a responsive advanced primary lesion without obvious metastases cannot be set. As stated, the initial process, even in the presence of distant and eventual progressive disease, not only can regress but may remain inactive for long periods after hormonal therapy. Thus, it may be more efficacious to continue the therapy until apparent maximum regression of the prostatic disease has been achieved. Consequently, individualization of treatment appears essential.

Scott and Benjamin[131] have mentioned certain fundamental requirements for the selection of patients as candidates for prostatectomy after estrogenic preparations: no evidence of distant metastases; local lesion caused by orchiectomy or stilbestrol therapy should be sufficiently diminished in size that a reasonable chance for complete removal exists; life expectancy should be at least three years on the basis of the patients' general condition. This combined approach is applicable, therefore, only in cases originally declared inoperable because of spread into the seminal vesicles or apex of the gland. Since the earliest signs of regression occur in the periphery of the growth, the spread in these areas may be reversed and the cases become operable.[140]

Mechanism of action. Again the question must be raised why an alteration in hormone balance should cause such pronounced changes in the natural evolution of a primary carcinoma and its secondary deposits. Huggins[136, 171] postulates that prostatic

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carcinoma in its early phases is not autonomous but is dependent on the presence of circulating androgens for its growth, and that castration or estrogen administration, by lowering the quantity and activity of circulating androgen, brings about a decrease in the size of the tumor and in the function of the cancer cells. In order to be susceptible to these methods of treatment, therefore, the tumors must be androgen-dependent and the testes must be contributing functionally significant amounts of the body's total androgen content. Huggins,[171] Scott and Vermeulen[172] and McCullaugh[6] have reported that after orchiectomy there may be a fall in urinary excretion of 17-ketosteroids, followed by a considerable increase for prolonged periods. The preliminary fall appears to be dependent on the removal of the gonads. Increased extragonadal production of androgens, presumably taking place in the adrenal glands as a result of increased pituitary stimulation, might account for the relapse after castration. Enlargement of the adrenal glands to several times their normal size has been described in patients no longer responding to treatment. Huggins surmises that carcinoma of the prostate eventually becomes autonomous and independent of androgens and so is no longer responsive to antiandrogen therapy. This was demonstrated by him in a unique study of the effects of bilateral adrenalectomy in 4 patients who had recurrence of prostatic carcinoma after an initial response to orchiectomy.[171] In the only patient who survived long enough to be studied under adrenal-substitution therapy, androgenic activity was apparently abolished, as has been determined by 17-ketosteroid determinations and comb growth in the capon. Nevertheless, the carcinoma progressed. Cox[173] noted similar results in 1 case. Thus, the premise of androgen independence appeared to be established. Total failure of castration and estrogen therapy in approximately 20 per cent of cases of advanced prostatic cancer could then be explained on the basis of primary androgen independence. With the availability of adrenocortical steroids and increasing knowledge of substitution therapy, bilateral adrenalectomy can now be performed with greater ease, and further studies of this aspect of the problem may be anticipated. Gahagen and Fischman[165] have utilized x-ray therapy of the adrenal glands on 10 patients who were unresponsive to estrogens and castration, reporting marked improvement in 3 of them.

Deming and Hovenanian[174, 175] have added further evidence to the theory of eventual androgen independence by the transplantation of human prostatic cancer into the anterior chamber of the eye of the guinea pig. They have been able to achieve successful takes only in male animals or in females stimulated by the injection of large doses of androgen, up to the eighth generation; after that the tumor will take in female animals not receiving androgen. The tissue appears to have become tolerant to estrogen and unsusceptible to the presence of androgen. Another evidence of a change in the metabolism and possible autonomy of the tumor pointed out by Deming is the initial decline of acid phosphatase when a tumor is responding well to the removal or inactivation of androgens and its subsequent failure to rise when the tumor is reactivated.

Wattenberg and Rose[176] have correlated the effectiveness of estrogenic therapy with the activities of prostatic cancer, which are secretion and growth. Such activities are unique except in tumors of organs of known endocrine function. The growth factor is influenced during estrogen therapy by changes in the secretory function, as measured by the acid phosphatase. If this is reduced by therapy, then treatment is assumed to have interfered with the growth of the malignant cells. In cancers with initially low secretory function but active growth function, estrogens would theoretically have less value. Another field for investigation is the demonstration of certain differences in the handling of exogenous estrogens between normal males and males with carcinoma of the prostate, which suggests the possibility of basic metabolic differences in such patients.[177]

Later studies have approached the possibility of androgen control therapy of prostatic cancer from another point of view. One of the authors and his colleagues reasoned that endogenous androgen production, presumably deleterious to prostatic cancer, might be effectively suppressed by the administration of similar steroid hormones through inhibition of androgen-stimulating hormones of the hypophysis.[178] It was also recognized that the use of those hormones with androgenic activity might through direct action temporarily accelerate the activity of the tumor but that with cessation of therapy the endogenous secretion would be materially reduced. In small series of cases[179, 180] actual symptomatic improvement during the administration of testosterone has been described. Evidence for this approach suggested that the rationale was justified.

Laboratory data indicated that nonandrogenic steroids other than estrogens might also depress androgen-stimulating hormones without directly activating the tumor. Here, too, the evidence suggests that suppression of certain pituitary secretions may cause diminution in androgen secretion and activity. Gutierrez[168] stated that progesterone was capable of producing further remissions in some cases eventually refractory to orchiectomy or estrogenic therapy. This has been studied and apparently confirmed by Trunnell and Duffy,[179] who utilized oral anhydro-hydroxy-progesterone and injectable progesterone. This use of progesterone in prostatic cancer was based on the premise that the hormone, as well as androgens, suppresses the release of the luteinizing hormone from the pituitary

gland. It has been postulated by some that the production of androgen by both testes and adrenal glands is controlled by the luteinizing hormone.[181] According to this theory, exogenous androgens and progesterone suppress endogenous androgen production, thereby inhibiting the growth of prostatic cancer. Some doubt has been cast on this theory as the major modus operandi by recent data acquired from the use of ACTH that makes the role of this hormone in androgen production debatable. The excretion rates of 17-ketosteroids usually increase after administration of adequate doses of ACTH. It is generally accepted that the 17-ketosteroids are excretion products of androgenic hormones. Thus, the possibilities of hormonal therapy in prostatic cancer are manifold. It must be considered that in cases no longer responding to one type of hormone therapy the residual tumor cells may have adapted themselves to become dependent on the environment created by the therapy. Under these circumstances, however, the tumor may have acquired vulnerability to effective therapy with other hormones. Hence, it appears that a shift in the endocrine status of the host may govern the response of a given tumor to hormonal agents.

The role of the pituitary gland in stimulating the adrenal glands to produce androgens after orchiectomy has been studied in the urinary excretion of gonadotropic hormone and 17-ketosteroids. It has been reported[141] that gonadotropins are excreted in increased quantities after orchiectomy, probably through lack of inhibitory actions of specific testicular hormones. Estrogen therapy decreases gonadotropic hormone excretion and in turn may diminish output of androgens. After orchiectomy there may be a rise in the 17-ketosteroids, presumably caused by pituitary stimulation of the adrenal androgens. There is rarely a rise in the 17-ketosteroids if estrogenic therapy is instituted immediately or shortly after orchiectomy. Thus, either technic appears to exert its effect through androgen suppression, but this does not rule out the possibility that other mechanisms are involved. Advocates of orchiectomy as the optimum procedure base part of their thesis on the argument that estrogens are incapable of effecting as complete a diminution in androgen secretion as does testicular removal.

Histologic changes. Histologic changes in prostatic cancer, judged by serial biopsies on patients receiving hormone therapy, have been studied extensively.[176, 182-184] Fergusson[135, 183] has followed some cases treated with estrogens and described a shift from the pattern of adenocarcinoma to a less cellular scirrhous form that on histologic analysis appeared to indicate a decrease in the diameter and number of nuclei per unit of tissue. Tissue acid phosphatase in the primary tumor and in metastatic nodes apparently decreases markedly after treatment. Unpublished data from our laboratory also indicate this. Fergusson could not correlate failure to respond to estrogenic therapy with any particular histologic entity.

Use of Sex Hormones in Tumors of Other Organs

Palliative therapy of selected cases of cancer of the breast and prostate gland by the administration of hormones has naturally led to their trial in other forms of cancer, particularly in organs related to the genital system.

Carcinoma of the uterus. Continued and unopposed estrogenic activity has often been incriminated in the development of uterine cancer, as it has been in breast cancer. The appearance of carcinoma of the endometrium in several patients who had been treated for some years with estrogen for menopausal symptoms has been reported.[185, 186] Ayre[187] believes, on the basis of vaginal and cervical cytologic studies, that about two thirds of patients with uterine carcinoma have high endogenous estrogenic activity. Additional studies in this direction are indicated. The association of malignant lesions of the uterus with estrogen-producing neoplasms of the ovary has been recognized frequently; it has been discussed in detail elsewhere.[10] In a series of 85 granulosa-cell and theca-cell tumors reported from the Mayo Clinic,[188-190] the incidence of uterine cancer was 17.2 per cent, a figure 100 times the expected coincidental occurrence. Endometrial carcinoma is rare in castrated females, whereas prolonged menstrual life and a history of atypical bleeding is common in victims of this disease.[191] Menopausal symptoms are often mild or absent in patients developing uterine cancer; this suggests the continuous production of small amounts of estrogen. It was, therefore, logical that testosterone should be tested in uterine as well as other types of female genital cancer. It is disappointing that present results have been unimpressive, suggesting again that most tumors behave differently in their response to hormones from normal tissue of apparently the same origin. Abel[192] has considered the possible basis of androgen therapy in gynecologic disease. In addition to the known activities of androgens, he took into account the ability of the androgens to inhibit gonadotropic activity of the hypophysis and the fact that androgens might nullify or modify activity of the estrogens. Accordingly, since several observers had reported that many patients with gynecologic types of cancer have increased gonadotropins, he explored the value of androgen therapy in malignant lesions of the female genital tract. Patients with advanced carcinoma of the endometrium, cervix, tubes and ovary were treated with androgens. They developed the usual signs of androgen administration, including a marked transient symptomatic improvement. There was no evidence of regression of the disease.

An excellent response of pulmonary metastases from carcinoma of the endometrium following testosterone administration has recently been re-

ported.[193] In this case the pulmonary lesions appeared to disappear completely for a period of six months, although osseous metastases were not obviously affected. The authors have recently noted, in a patient receiving large doses of progesterone, apparent regression of pulmonary metastases, presumably from a carcinoma of the endometrium, locally controlled by other measures. Two other patients similarly treated have shown no response.[194]

Carcinoma of the cervix. We have treated a small series of cases of cervical carcinoma with extensive metastases with estrogens and androgens. One patient bedridden with hepatic and osseous metastases showed an excellent clinical response to estrogen therapy for a period of ten months. She became comfortable and was able to walk. The liver diminished markedly in size, but there was no demonstrable effect on the osseous metastases.[194] The other cases showed no response. Nieburgs[195] has recently observed apparent regressive changes in some cases of cervical cancer with the use of estrogen therapy.

Hertz and his colleagues[196, 197] have treated cervical carcinoma with large doses of progesterone. This was based on evidence from animal studies that progesterone suppressed the growth of estrogen-induced cervical lesions of various kinds. These workers noted visible and palpable evidence of regression of the primary lesions in 11 of 17 patients with early to moderately advanced lesions. Most of their patients subsequently underwent radical surgery. The authors have treated a few patients with far advanced disease in a similar manner; a definitive beneficial response has been observed in only 1. It should be emphasized that the stage of the disease at the time that treatment is instituted is important in the evaluation of the effects of hormonal therapy, as in the use of x-ray or surgical therapy. It is entirely possible that the early lesions have not achieved the autonomy of more advanced stages and thus may be more susceptible to hormonal therapy. This may account for the variation in response reported by various observers.

Carcinoma of the ovary. Wyatt[198] failed to note any retrogression of carcinoma in 2 patients with ovarian cancer treated with large doses of testosterone propionate. Chaney and Greenblatt[199] treated three cases of primary ovarian carcinoma with testosterone. They state that in addition to symptomatic improvement there was a diminution in the size of the tumors, as noted on palpation and confirmed by exploration. They concluded that testosterone is a valuable palliative measure in such cases. We have treated several cases with androgens without significant objective results, although a few showed symptomatic improvement that can probably be explained by the metabolic effects of androgens.

Estrogen therapy has been employed in 8 patients with extensive ovarian carcinoma with metastases, 3 of whom have shown interesting responses. One of these had a previously x-ray-sensitive ovarian carcinoma recurring over a ten-year period in the pelvis, abdomen and distant nodes. She was given stilbestrol when, six months after her last x-ray treatment, she developed ascites, liver enlargement, partial stenosis of the rectum and multiple cervical and axillary nodes. Further x-ray therapy was considered unwise at this time. Within three months ascites, nodes, rectal shelf and hepatic enlargement disappeared. This status has been maintained under stilbestrol therapy for three and one-half years. A second patient appeared to have regression of multiple pulmonary metastases under treatment with estrogens, but cerebral metastases developed simultaneously. Our third patient, a woman with extensive abdominal carcinomatosis, had four months of complete freedom of symptoms under estrogen therapy before ascites recurred and a rapid downhill course ensued.[194]

Carcinoma of the bladder. Since the bladder and the prostate gland have a similar embryologic origin, estrogens have been administered to males with advanced cancer of the bladder.[2, 200] Beneficial clinical improvement has been noted in a few patients, although the cystoscopic picture has remained unchanged.[200] The most consistent effect is said to be a symptomatic reduction of vesical irritability. It is claimed also that papillomas have disappeared. Although anaplastic tumors are clinically unaltered, low-grade tumors may show cytologic changes claimed to be identical with those seen in cancer of the prostate gland treated with stilbestrol. On the same basis of reasoning, Shivers[201] and Hebert[202] have treated 6 cases of extensive cancer of the bladder with castration; in all cases they noted relief of pain, frequency and hematuria, with apparent improvement in cystoscopic appearance. These observations warrant further investigation.

Chorionepithelioma. In an attempt to depress gonadotropins of chorionic origin by the administration of estrogens and thus to achieve a favorable influence against rapidly growing metastatic chorionepithelioma, two female patients with this disease have been treated with stilbestrol.[203, 204] Temporary subjective and objective improvement was observed in both cases, and diminution in output of gonadotropic hormone was demonstrated.[204]

Miscellaneous tumors. The authors and others have attempted to influence the course of cancer of other organs by the administration or suppression of sex hormones. The logic of this approach stems from sex differences in the incidence of cancer in sites other than those that are apparently sex-linked. With few exceptions, cancers common to both sexes are significantly more frequent in the male. On this

basis, primary suppression of, or the administration of an antagonist to, the dominant sex hormone might be expected to produce a favorable reaction. A series of advanced pulmonary, gastrointestinal and other neoplasms have been subjected to either castration or hormone administration with no objective change, even though temporary subjective responses to hormonal administration have occurred in some patients. Primary osseous tumors were treated by estrogen, androgen or a combination, because of their effects on bone metabolism and growth. No demonstrable changes were observed.

Therapy of Cancer with ACTH and Cortisone

In the past two years, with the availability of increased quantities of ACTH and cortisone, these agents have received extensive trial in various forms of neoplastic disease. The results are not so impressive as was initially anticipated, although transient beneficial effects and occasional dramatic remissions in certain types of malignant disease have been reported. The first published results reported the trial of these agents in leukemia and lymphoma.[205-207] There were good theoretical reasons for assuming that stimulation of adrenal steroids by ACTH or cortisone might elicit a favorable response in these two diseases. Among these reasons are the well established observations that increased adrenal cortical function in animals produces involution of lymphoid tissue[208] and Dobriner's findings of altered urinary steroid excretion in patients with such diseases.[209] Pearson and his co-workers[206] reported the results of treatment with ACTH and cortisone of 6 patients with chronic leukemias and malignant lymphomas of various pathologic types. They noted temporary reduction in size of involved lymph nodes and spleens lasting for from ten days to three months after completion of therapy. Excellent but short-lived clinical and hematologic remissions of more impressive degree were then produced in a few cases of acute lymphatic and myelogenous leukemia. Since these preliminary reports appeared, longer series of cases with various lymphoid and hematologic dyscrasias have been treated with ACTH or cortisone for periods of a few days to several weeks.[12, 210-229] There appears to be no significant difference in response to the two agents. From the data now available on a substantial series of patients, it may be concluded that complete or partial remissions lasting from a few days to several weeks may follow the administration of either ACTH or cortisone in a moderate number of cases of acute and subacute leukemia. The bone marrow may revert temporarily to a state indistinguishable from normal. The most favorable results have been achieved in children with a lymphatic type of leukemia. Occasional responses have been reported in acute myelogenous, eosinophilic and monocytic leukemias,[215, 226] but it should be recognized that the classification of the primitive cell types that often dominate the marrow in acute cases is difficult and subject to varied interpretation. Dameshek, Rosenthal and others[210, 216] have reasoned that granulocytic leukemias might be accelerated by the administration of these preparations because of their stimulating effects on all series of marrow cells; they present clinical evidence to justify this theory. In a few cases of chronic lymphatic leukemia subjective improvement, decrease in lymphadenopathy, splenomegaly and hematomegaly have occurred. These cases have shown an initial substantial rise in peripheral lymphocyte count, often followed by a fall to or below pretreatment levels. No alteration in marrow in these cases has been demonstrated. Short-lived partial remissions in symptoms and signs of Hodgkin's disease, lymphosarcoma, leukemia cutis and mycosis fungoides have been observed, although no significant pathologic alterations have been found in serial biopsies in most cases. In one case of lymphosarcoma, however, Taylor[214] reported progressive fibrosis and necrosis during therapy with cortisone. The patients with this group of diseases who have responded favorably have shown a reticulocytosis and a rise in hemoglobin. It should be emphasized that acceleration of the disease process in certain cases has been attributed to these drugs. In addition to possible acceleration of myelogenous leukemia, already mentioned, the authors have seen rapid decline and probably premature death in a case of advanced Hodgkin's lymphoma and in one of lymphocytic lymphoma.

It is of great interest that acquired hemolytic anemia, which not infrequently complicates advanced lymphoma, lymphosarcoma and chronic leukemia, can be dramatically improved by the administration of ACTH.[216, 230, 231] Such patients have shown almost complete remission of the hemolytic process, with decline in the titer or disappearance of abnormal agglutinins as determined by the Coombs test. We have studied 2 patients with acquired hemolytic anemia complicating metastatic carcinoma of the breast and Hodgkin's disease respectively in whom ACTH was totally ineffective on either process. However, under cortisone therapy an excellent remission of the hemolytic process occurred, with marked diminution in the Coombs titer. It is suspected that these 2 patients may have disease in the adrenal glands. A few patients with acquired hemolytic anemia reported by others have shown fairly prolonged remissions on maintenance therapy. Three of our patients have remained in sustained remission six months after cessation of therapy.

Multiple Myeloma

Approximately 20 per cent of a small series of cases of multiple myeloma have been benefited by ACTH or cortisone.[211, 214, 216, 217, 223-225, 229] Responses have been characterized by improvement or complete relief of pain, increase in strength and well-

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being, significant increases in hemoglobin and hematocrit, decreases in serum total protein and globulin amounting in some instances to several grams, marked decline in excretion of Bence-Jones protein, decrease in total percentage of marrow plasmablasts and shift to the right in remaining plasmacytic elements. No change in osseous lesions has been seen by x-ray. Although most of these responsive patients have relapsed within a short time after cessation of several weeks of therapy, a few had remissions for almost a year. This type of response appears to be most common in the patient in whom the disease is characterized by a predominance of plasmablasts and proplasmacytes rather than of mature "myeloma" cells.

Miscellaneous Tumors

Because of a potential depression of fibroblastic proliferation under the influence of ACTH and cortisone administration, a beneficial effect on neoplastic disease of connective-tissue origin might be anticipated. Unfortunately, such an effect has not been seen. A few cases of fibrosarcoma, neurofibrosarcoma, rhabdomyosarcoma, malignant melanoma, synovioma, neuroblastoma, osteogenic sarcoma and Ewing's tumor have been treated by us and others without demonstrable effect on any of the tumors.[214, 218, 222] Several of these patients have enjoyed the transiently stimulating effects of the hormones. Certain patients with extensive pulmonary metastases have shown diminution in dyspnea and cough and some increase in vital capacity during the treatment period, probably attributable to reduction in the inflammatory reaction excited by the lesions. Microscopical study has demonstrated no significant changes.

Since atypical excretion of steroids presumably of adrenal origin has been found by Dobriner[111, 116] and others in several forms of neoplastic disease, — particularly of breast and prostatic origin, — ACTH and cortisone have been tested as therapeutic agents in a variety of neoplastic lesions. They have been ineffective against several types of carcinoma, including carcinoma of the breast, prostate, esophagus, gall bladder, stomach, colon, trachea, cervix, kidney, pancreas, testis, adrenal gland and lung.[206, 211, 214, 221, 222, 232-234] Again, in a few cases, a transient tendency toward healing of carcinomatous ulcers of the breast has been noted, probably due to reduction in inflammatory reaction. Further trials are under way in all these types of tumors.

Urinary steroid-excretion patterns in patients with various forms of neoplasm under treatment with ACTH and cortisone have been studied.[209, 235] There is great individual variation among the patients. In general, the results have revealed an increased excretion of metabolites of the C-19 and C-21 series, with and without 11-oxygen function. A variety of unidentified compounds not present in the urine of normal or diseased persons has been found. Such investigations are of great interest and may be of considerable significance as the number of studies is increased.

Toxic Effects

The unfavorable effects accompanying the administration of ACTH and cortisone are variable. They are in part dependent on dose level, length of treatment period and the physiologic and mental status of the patient. Alterations in electrolyte and fluid balance, carbohydrate and protein metabolism, blood pressure, mental status and wound healing that may be produced by these agents have been widely discussed elsewhere. These agents should be used only in full cognizance of the possible complications and unfavorable reactions.

Summary

From the reports available, it must be concluded that ACTH and cortisone have extensive potentialities for research and limited therapeutic application in the field of cancer. Their therapeutic use is at present limited to carefully selected neoplasms of the lymphoid and hematopoietic systems. In the majority of cases, it appears that they should be regarded as supplements to, rather than substitutes for, established therapeutic measures. Their utilization for nonspecific stimulating effects in patients with nonresponsive tumors is mentioned only to be decried. As research tools they hold promise of elucidating further the nature of the reaction of the organism to the presence of neoplasm.

Conclusion

There is indisputable evidence in the data here reviewed that the administration or deprivation of steroid hormones may profoundly alter the natural evolution of certain types of malignant disease. As investigation continues it becomes increasingly obvious that endocrine therapy singularly affects only certain types of tumors. This implies a unique specificity that is related to the intrinsic characteristics of the cells influenced rather than an effect on neoplastic growth in general. Their use as therapeutic agents is limited to those cases in which more generally accepted measures have failed or are not applicable by reason of the nature of the tumor or of its spread. The sex hormones may be adjuncts to the treatment of advanced carcinoma of the breast, prostate, cervix and uterus. ACTH and cortisone have limited value in the therapy of acute leukemia, myeloma and malignant lymphoma.

It is anticipated that the increasing utilization of known compounds and development of new steroidal agents will open new avenues toward a better understanding of the biologic characteristics of cancer.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38051

PRESENTATION OF CASE

A fifty-two-year-old woman was admitted to the hospital because of severe dyspnea.

Nineteen years before admission the patient was in the hospital after a miscarriage. Examination then revealed marked cardiac enlargement, signs of mitral stenosis and regurgitation, a hemoglobin of 5.5 gm. and right-bundle-branch block. The anemia responded to iron and liver therapy and for the next ten years she had mild exertional dyspnea; she was able to carry out her household duties and slept on one pillow. Eight years before entry she was in another hospital because of a sore throat and stiff, swollen joints; the clinical diagnosis was acute rheumatic fever with pericarditis and congestive failure. She was sick for approximately six months, during which time she had a low-grade fever. Since then she had taken digitalis, one tablet daily. During the seven to eight years prior to entry she was well, except for mild exertional dyspnea and occasional attacks of palpitations and dyspnea. The latter were sometimes accompanied by a sudden knife-like pain in the lower substernal region and the left base of the neck; there was no radiation to the arms, and the attacks passed off within two hours. Four years before entry she was in another hospital because of a severe attack of this pain; during this admission she noted that on several occasions physicians became alarmed about her pulse, even though at those moments she felt nothing unusual. Five weeks before entry she had a sudden attack of marked palpitation, which was followed by dyspnea and a feeling of faintness, lasting again about two hours. Since then she had been markedly fatigued and had noted a peculiar feeling of "light-headedness." Two weeks before entry the blood pressure was 130 systolic, 98 diastolic and an electrocardiogram was normal. Five days before entry palpitations recurred, and she developed increasing dyspnea and 5-pillow orthopnea. These symptoms persisted with some fluctuations in intensity.

At the age of twenty-four she had had a severe attack of acute tonsillitis accompanied by swelling of her joints.

On physical examination the neck veins were pulsating in the sitting position. There was a malar flush. Scattered moist medium rales were heard at both lung bases. The heart was enlarged, with the apex at the anterior axillary line. The rhythm was regular. The heart sounds were distinct, and the pulmonary second sound was louder than the aortic. Murmurs were difficult to identify at the rapid rate, but a Grade II aortic systolic murmur and a Grade II apical diastolic rumble without presystolic crescendo were heard. A slightly tender liver was felt 2 fingerbreadths below the right costal margin. There was no peripheral edema.

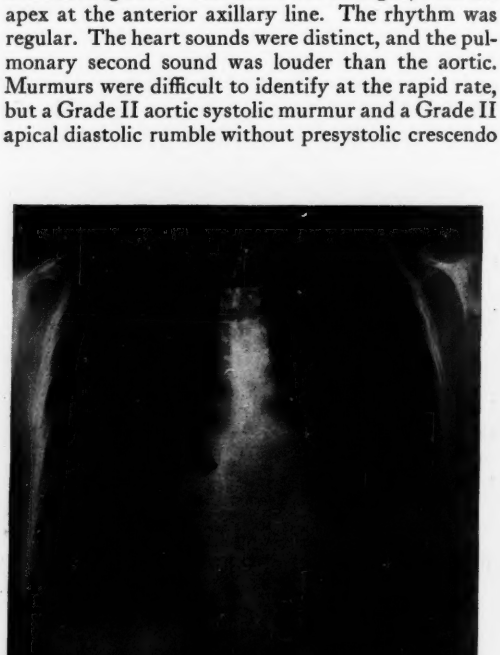

FIGURE 1. *Roentgenogram of Chest.*
Dotted arrow points to displacement of esophagus; solid arrow points to elevated left main bronchus.

The temperature was 100°F., the pulse 140 and the respirations 40. The blood pressure was 110 systolic, 70 diastolic.

Urinalysis showed a specific gravity of 1.014, with a rare red cell, white cell and granular cast in the sediment. Examination of the blood revealed a hemoglobin of 14.6 gm. and a white-cell count of 9200, with a normal differential. The serum sodium was 134.3 milliequiv., the chloride 102 milliequiv., the carbon dioxide 27.4 milliequiv. and the potassium 4.2 milliequiv. per liter; the nonprotein nitrogen was 27 mg. per 100 cc. An electrocardiogram showed auricular flutter with a 2-to-1 block. A roentgenogram of the chest (Fig. 1) showed marked

cardiac enlargement, with a prominent left ventricle. The left auricle was enlarged and displaced the esophagus to the right and posteriorly. No intracardiac calcification was seen at fluoroscopy, and the lung fields showed an almost normal degree of vascularity. A small amount of fluid was present at the right base.

The patient was given 0.4 mg. of Cedilanid intravenously and 1 cc. of Mercuhydrin intramuscularly. Five minutes later the heart rate was 100; 15 minutes later it was 75. She was then more comfortable and the dyspnea was much improved. After this, a coarse loud aortic systolic murmur, a diastolic blow along the left sternal border and a rumbling apical diastolic murmur were discernible. The day after admission an electrocardiogram showed a normal rhythm at a rate of 80, a PR interval averaging 0.22 second, occasional auricular premature beats and left-bundle-branch block. She was treated with digitoxin and quinidine sulfate (for six days). From the third day on, the temperature rose to 100°F. daily. On the sixth day she had a "faint spell" without palpitation and developed tachycardia, hypotension and sweating. An electrocardiogram showed a rate of 130, with irregular sinus rhythm and obscure P waves. Later she again felt better and her extremities were warm and moist. The pulse varied between 80 and 120 and the blood pressure was 95 systolic and questionably 80 diastolic. A few crepitant rales were heard at the left lung base, and the neck veins pulsated slightly. Morphine and intravenous Cedilanid were given. The next morning the blood pressure was 115 systolic, 80 diastolic, the heart sounds were faint and the murmurs were poorly heard. An electrocardiogram showed sinus tachycardia at a rate of 105; a PR interval of 0.20 second; a QRS interval of 0.13 second; tall broad P waves in Lead 2; and left-bundle-branch block. The P waves were tall and broad in Lead 2; the T waves were upright in Leads 1, 2, AVL, AVF, V_1, V_2, V_3, V_4 and V_5 and diphasic in Leads 3 and V_6. On the sixth hospital day, while lying in a semirecumbent position, she had an episode of faintness associated with right-upper-quadrant discomfort; two and a half hours later she was feeling well and on examination the heart was unchanged, the abdomen was soft and nontender and the liver was not felt. On the eighth day the temperature rose to 102°F.; she felt well, her pulse remained below 100 and physical examination was unchanged. On two occasions during the previous three days there had been a suggestion of a friction rub at the apex. Two blood cultures showed no growth. On the ninth hospital day she was found dead in bed; one hour previously she had appeared well and had eaten her supper.

Differential Diagnosis

Dr. Robert S. Palmer*: I come once again to what Dr. Edward D. Churchill is pleased to call a public guessing game.[1,2] I disagree with him very strongly. I think that by intelligent consideration of the evidence we ought to be able to include in the differential diagnosis what actually happened. I suggest that these conferences are public examinations by our peers to determine whether or not we are competent to take care of patients with mortal disease. Now we shall see.

This woman's trouble began when she was twenty-four years old, with a severe attack of tonsillitis accompanied by swollen joints. I know from the history and the physical signs that this patient had rheumatic heart disease and recurrent rheumatic infection, and that at one time she had a long recurrence, with rheumatic pericarditis. The lower substernal pain with radiation into the neck suggests aortic valvular involvement and interruption of blood flow to the coronary arteries and hence the possibility of aortic stenosis. Light-headedness may accompany aortic stenosis. If the murmur was loud and associated with a thrill and the aortic second sound was absent, then the patient did have aortic stenosis. The enlargement of the heart to the left is consistent with aortic valvular disease. I suspect, however, that the aortic valve was stiffened but not to the degree that I would call aortic stenosis. The apical diastolic rumble makes me think the patient had mitral stenosis. I wonder if in addition she may have had tricuspid-valve disease and whether or not such tricuspid disease may have been organic or functional. The patient had increased venous pressure and may have been sparing herself by engorging the liver, as patients with mitral stenosis do. At any rate, this is the case of the phantom liver; first it was felt two finger-breadths below the costal margin and then it was not. This suggests not necessarily organic but possibly functional tricuspid regurgitation. That is the way a patient with rheumatic heart disease gets rid of the extra fluid or pressure in the chest. There was nothing typical, such as a large liver or ascites or a loud low sternal murmur, to make me think that she had organic tricuspid disease.

I should like to ask Dr. McCort if there was a large superior vena cava, what the size of the liver was and whether or not there was calcification in the aortic valve. I shall also ask him if he can tell from the shape of the heart whether this left-ventricular hypertrophy or any such hypertrophy can be called characteristic of aortic stenosis rather than of aortic regurgitation.

Dr. James J. McCort: The heart is grossly enlarged and extends to the lateral wall of the left chest; it is boot shaped, and the left ventricle must be considered to be enlarged. On the lateral film we see that the heart extends to the anterior chest wall, so the right ventricle may be enlarged or may be pushed anteriorly by the large left ventricle. The barium-filled esophagus is displaced to the right and posteriorly (dotted arrow) by the large left atrium, which also elevates the left main

*Physician, Massachusetts General Hospital.

bronchus (solid arrow) (Fig. 1). No intracardiac calcification is seen on the films. I do not believe the lung fields are abnormally clear.

DR. PALMER: That is very helpful.

DR. MCCORT: If anything, the lungs show a slightly more than normal vascularity, but the pulmonary artery is not dilated. No widening of the superior vena cava can be made out. A small amount of fluid is present in both costophrenic sinuses. There is no evidence of old or recent pulmonary infarcts, although this possibility is not entirely ruled out, since the lower half of the left lung is obscured by the large heart. I cannot give you any information about the size of the liver, as only films of the chest are available, but the right leaf of the diaphragm is not elevated to any degree.

DR. PALMER: Are you one of those who hold that they can tell by careful examination of the configuration of the heart whether there is more stenosis than regurgitation or more regurgitation than stenosis of the aortic valve?

DR. MCCORT: I do not believe I can determine that accurately.

DR. PALMER: The lung fields are rather surprisingly clear if they are not abnormally clear. It may be that this patient was able to engorge the liver at times to relieve the pulmonary congestion.

What do I know that this patient had, in addition to the rheumatic heart disease with aortic regurgitation and mitral stenosis? I know that during the final illness she had a temperature, which makes me think about infection — recurrent active rheumatic infection, perhaps pericardial, or subacute bacterial endocarditis. The physicians who cared for this patient were thinking of a subacute bacterial endocarditis when they took the blood culture. Although they did not find any organisms, that is not necessary. However, the illness was rather short, and there was nothing typical that leads me to believe this patient had subacute bacterial endocarditis.

This was a sudden and unexplained death, although it occurred under observation here at the hospital. I have five suggestions to make and hope and expect that among them will be the actual cause of death — if Dr. Castleman was able to determine it. First, disorder of rhythm; anybody who has a disorder of cardiac rhythm may have cardiac standstill, and if she did, nothing will be shown as the cause of death.

Secondly, patients with aortic stenosis die suddenly and unexpectedly. I suppose it is possible that this patient had aortic stenosis, but there was no x-ray evidence of calcific aortic stenosis and there was not an absent second sound. At least it was not specifically mentioned as being absent. Therefore I am going to choose to believe that this patient had a stiffened or deformed aortic valve rather than the true, meaningful, very tight aortic stenosis that is sometimes associated with sudden death.

Thirdly, this patient could have died with a massive pulmonary embolus. We all know that thrombophlebitis is very common, especially in patients of this age who are in bed and who have failure of the heart. If pulmonary embolus was thought to be present or possible, I am going to ask why nothing was said about anticoagulants or vein tying. Such therapy may have been considered but not used for good reason.

Fourthly, the commonest condition associated with left-bundle-branch block at this patient's age is coronary sclerosis. The pain that she had as she grew older may indicate coronary disease, even in the presence of rheumatic heart disease. Could the pericardial rub described as heard at the apex only a day or two before the patient died represent a myocardial infarct?

Finally, the most common cause of sudden death, other than cardiac standstill, is rupture of the heart. For many years physicians have been trying to make a diagnosis of atrial infarct, which may rupture and cause cardiac tamponade. This is the first opportunity I have had to attempt to make such a diagnosis with reasonable hints. That notoriously inaccurate science, electrocardiography, sometimes gives such hints. I should like to invite your attention to the changing PR interval, the paroxysmal flutter, the auricular extrasystoles and the change in the configuration of the P waves.

DR. CONGER WILLIAMS: One thing that was not emphasized in the protocol was the fact that this patient was quite well from the time she was first seen by Dr. Paul D. White and Dr. Edward F. Bland, — a period of twenty years, — with the exception of the acute episode requiring hospital admission four years before entry here. Twenty years before admission, Dr. White and Dr. Bland made the diagnosis of high-grade mitral stenosis, regurgitation and cardiac enlargement. I do not believe she had heart failure at that time, but the heart was described as being at the anterior axillary line. Since then she had had almost no congestive failure until the recent complication of auricular flutter brought her into the hospital. When I saw her first in the office she was obviously in congestive failure. I have the electrocardiogram here. It shows auricular flutter with 2:1 heart block and a ventricular rate of 150. We thought of tricuspid disease, but the neck veins lacked the usual characteristics seen in tricuspid regurgitation — namely, a deep jugular pulse with a plateau characteristic. There was no typical murmur at the left sternal border that could be described as originating in the tricuspid area. The acute episodes she had in the hospital I thought were due to ball-valve thrombus. None of us happened to be there when they occurred. They were consistent, in that she had slowing of the pulse, described by the nurse, fall in

the blood pressure, increased dyspnea and apprehension. We thought she might have had pulmonary emboli, too, but we were never able to make that diagnosis and therefore did not give her anticoagulants, nor did we have the veins tied.

DR. PALMER: Are not patients with a ball-valve thrombus often cyanotic, frequently showing patchy peripheral blotches on the finger tips? Don't they pass out and fall down?

DR. WILLIAMS: That depends on how complete the obstruction of the valve orifice is and how long it lasts.

DR. REED HARWOOD: There was one condition you did not suggest — the finding at autopsy of a heart full of myocardial Aschoff bodies. When I was an intern we had a patient with a fever of unknown origin. We allowed her to dress to go home, and she died in the dressing room quite suddenly. All Dr. Castleman could find were many Aschoff bodies in the myocardium.

DR. PALMER: That would come under rheumatic infection.

CLINICAL DIAGNOSES

Rheumatic heart disease.
Ball-valve thrombus.

DR. PALMER'S DIAGNOSES

Rheumatic heart disease with mitral stenosis and aortic regurgitation, rheumatic pericarditis.
?Cardiac standstill.
?Massive pulmonary infarction.
?Rupture of the heart due to atrial infarction.
?Coronary thrombosis with infarction.

ANATOMICAL DIAGNOSES

Rheumatic heart disease with mitral, aortic and tricuspid stenosis and regurgitation, marked.
Sudden death, ?cardiac arrhythmia.
Cardiac hypertrophy and dilatation, severe.
Rheumatic myocarditis and pericarditis, old.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The heart in this case was enormous, weighing almost 800 gm. The largest chamber was the right auricle, which was tremendous, although the other chambers were both dilated and hypertrophied. Three valves were involved, the mitral, aortic and tricuspid. The mitral was slit-like and fish mouthed but showed no calcification. The chordae tendineae were very short and thick. The aortic valve measured about 0.5 cm. in diameter and was fused, thickened and stiff but not calcified; I am sure there must have been both stenosis and regurgitation. The tricuspid valve also showed shortening and thickening of its chordae tendineae and was probably less than half the circumference seen in a normal valve. The coronary arteries were perfectly clear; they showed very little atheroma and no evidence of any occlusion or narrowing. The myocardium in the gross looked normal. There was extensive endocardial thickening in the left ventricle just below the aortic valve, with perhaps an attempt to form a fourth cusp. This, with flattening of the trabeculae carneae in the left ventricle, I consider pretty good evidence of regurgitation. Microscopically the myocardium showed scattered foci of fibrosis with some cellular infiltration — scars believed to be the result of old rheumatic myocarditis but nothing recent. The pericardial cavity was completely obliterated by an old rheumatic pericarditis. That is all we found. There was no ball-valve thrombus. There was a very small embolus to one of the terminal branches in the lung but certainly not anything that would produce sudden death. There was no pulmonary infarction and only minimal congestion in the lungs. The liver showed evidence of central congestion and some necrosis.

I believe she had a ventricular standstill or something of that nature — perhaps associated with aortic stenosis or perhaps with some defect in the conduction system as a result of the endocardial fibrosis and the fairly extensive myocardial fibrosis.

DR. WILLIAMS: The degree of tricuspid stenosis was extreme. I have never seen it this great. I would not think I could have put the tip of my little finger through it at the very apex. The base looked pretty normal. It was a cone that narrowed down to nothing.

DR. PALMER: You did not tell me about the right auricle, Dr. McCort! Should it not bulge the esophagus opposite to the bulge from the left auricle?

DR. MCCORT: The heart was generally enlarged; when it comes to picking out the largest of the four chambers from the film, I would still think the left ventricle was the largest.

In this patient I interpreted the deformity of the esophagus as due to the enlarged left auricle. How much, if any, of this deformity is the additional result of right-auricular enlargement I do not know.

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CASE 38052

PRESENTATION OF CASE

First admission. A sixteen-year-old girl was admitted to the hospital because of swelling of the legs.

Two years prior to admission there was a four-day episode of abrupt onset during which she had general malaise, a nonproductive cough, urgency, frequency (10 to 15 times) and nocturia (4 to 5 times). There were no chills, fever, hematuria or edema. Three weeks later a sore throat developed, all the above symptoms recurred and in addition the

urine became definitely cloudy. The latter gradually cleared, but the malaise, frequency, nocturia and urgency of varying degrees persisted. A year and a half prior to admission there was the gradual onset of swelling of both ankles. Shortly after this she was in another hospital for seven weeks for colicky right-lower-quadrant pain, occasional nausea and clay-colored stools. She was told that she had "yellow jaundice." Hypertension and "blood cells" in the urine were noted at this time, and she was placed on a high-protein, low-salt diet, which she had followed since then. The frequency, nocturia and urgency diminished, but she continued to have mild persistent ankle edema and malaise, and over the subsequent months she developed occasional morning frontal headaches and mild exertional dyspnea.

Two brothers, twenty-one and nineteen years of age, had hypertension, the onset of which began with convulsions, and her mother had been known to have hypertension for five years. Her father had died of tuberculosis when she was seven years old.

Physical examination revealed a well developed, well nourished girl in no distress. The fundi were negative. The neck veins were flat. The lungs, heart and abdomen were normal. There was fairly marked pitting edema of both lower extremities up to the knees.

The temperature was 99°F., the pulse 100 and the respirations 16. The blood pressure was 170 systolic, 116 diastolic.

The urine gave a ++ reaction for albumin; there were frequent granular casts, 25 red and 40 white cells in the sediment. The maximum urinary concentration was 1.012. Cultures of the urine showed no growth. The urinary output of protein was 3.46 gm. per twenty-four hours. Examination of the blood showed a hemoglobin of 12.2 gm. and a white-cell count of 10,000. The nonprotein nitrogen was 27 mg., the cholesterol 320 mg. and the total protein 5.24 gm. per 100 cc., with an albumin-globulin ratio of 0.8. A phenolsulfonphthalein-excretion test showed normal ability to excrete the dye. Roentgenograms of the chest showed a prominent left ventricle. An intravenous pyelogram could not be performed because of Diodrast sensitivity.

The patient was treated with a high-protein, low-salt diet and responded well, with a decrease in the edema and an eight-pound weight loss. She was discharged after ten days.

Second admission (two months later). In the interval the patient was on a modified rice diet. The edema had been generally minimal, but the blood pressure had remained elevated. Two weeks prior to admission the swelling of the legs increased, extending to above the knees. She had had no headaches, hematuria or oliguria.

Physical examination was unchanged, except that the abdomen was somewhat distended and tense and shifting dullness could be demonstrated. The blood pressure was 165 systolic, 120 diastolic.

The urine gave a ++++ reaction for albumin; the sediment contained many red cells, white cells and granular casts. The serum total protein was 4.11 gm., with an albumin-globulin ratio of 1.2, and the serum cholesterol 888 mg. per 100 cc. A urea-clearance test gave values of 43, 34 and 34 per cent of normal.

On bed rest and strict adherence to a low-sodium, high-protein diet the patient lost 4 kilograms of weight and improved somewhat symptomatically. She was discharged after four weeks.

Third to seventh admissions. Over the subsequent eighteen months she was admitted to the hospital five times at intervals varying from one to five months. Each of these was for the reappearance of marked edema, which eventually involved the hands and periorbital tissues as well as the legs and abdomen. Finally she began to have dyspnea and orthopnea with the edema, and on some of these admissions she had pleural effusions by x-ray examination. On the third admission minimal hypertensive changes were seen in the fundi, and by the seventh admission there was papilledema and some recent hemorrhages in the fundi. The blood pressure remained unchanged. On many of the admissions she had a protodiastolic gallop and systolic murmurs, in addition to edema and abdominal distention.

The urinalyses were essentially unchanged. On examination of the blood during the seventh admission, the hemoglobin had dropped to 10 gm. The nonprotein nitrogen steadily rose from 36 mg. per 100 cc. on the third admission to 90 mg. per 100 cc. on the sixth and 140 mg. per 100 cc. on the seventh. The serum cholesterol varied between 258 mg. and 572 mg. per 100 cc. The serum total protein was 4.25 gm. per 100 cc., with an albumin-globulin ratio of 0.5 on the third admission, and the twenty-four-hour urinary excretion of protein varied between 3.2 and 23.7 gm. per 100 cc. A urea-clearance test on the third admission was 22 per cent of normal. At the seventh admission the serum sodium was 123.9 milliequiv., the chloride 98 milliequiv., the potassium 6.3 milliequiv. and the carbon dioxide 14.6 milliequiv. per liter; the calcium was 8.6 mg. and the phosphorus 10.4 mg. per 100 cc. A twenty-four-hour urine specimen contained 1.3 milliequiv. of sodium, 10 milliequiv. of chlorides and 32 milliequiv. of potassium per liter.

On subsequent admissions the patient was treated by diet, diet and nitrogen mustard and digitalis and Mercuhydrin. By the sixth admission she was refractory to these methods but improved somewhat with Southey tubes. At the seventh admission she responded only moderately well to Southey tubes and showed no response after four days'

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ACTH therapy. These admissions varied between three weeks and three months in length.

Final admission (age nineteen — six weeks after previous discharge and three years after the first admission). At the time of the previous discharge there remained a moderate amount of peripheral edema, and there was a rash on each leg from the Southey tubes. Three days prior to admission the rash on the right leg "broke down" and began discharging, with the formation of large blisters. Two days prior to admission the arms and legs began to swell, and she noted increasing dyspnea. On the day before admission she noted periorbital edema, severe dyspnea and anorexia with some vomiting.

Physical examination revealed a weak, pale, lethargic girl, racked by frequent retching. There was anasarca, with massive leg edema, pitting edema of the back and hands, puffiness of the lower face and periorbital edema. There was marked retinopathy, as previously described. The lungs showed dullness to percussion bilaterally, with bronchial breathing and rales throughout. The heart seemed enlarged, with a pulsus alternans and a gallop rhythm. The abdomen was tense and rounded, with a fluid wave. There were superficial ulcerations over both tibias.

The temperature was 98°F., the pulse 112 and the respirations 24. The blood pressure was 195 systolic, 150 diastolic.

The urine had a fixed specific gravity of 1.010 and gave a constant ++++ reaction for albumin; the sediment contained an occasional red cell. Examination of the blood showed a hemoglobin of 12.0 gm. and a white-cell count of 14,400, with 90 per cent neutrophils. The nonprotein nitrogen was 164 mg. and the total protein 5.35 gm. per 100 cc., with an albumin-globulin ratio of 1.6; the serum sodium was 124 milliequiv. and the potassium 7.2 milliequiv. per liter.

There was little response to treatment with low-sodium diet, calcium gluconate, digitalis, Gelusil and Bacitracin ointment on the legs. Three weeks after admission she developed a pericardial friction rub, loudest in the mitral area, and four days later a pleural rub was heard at the right base laterally. She became increasingly drowsy and anorexic and died quietly on the thirty-fourth hospital day.

Differential Diagnosis

Dr. John D. Crawford*: My working diagnosis in this case is subacute glomerulonephritis, which progressed through the nephrotic syndrome to terminal uremia. The differential diagnosis should include pyelonephritis, hypertensive nephrosclerosis and renal vascular anomaly. The diagnosis of pyelonephritis is untenable in view of the several negative urine cultures. I shall rule out nephrosclerosis on the basis of the facts that we have no knowledge of hypertension preceding the kidney disease and that this degree of albuminuria and edema is uncommon in that condition. At an exercise such as this, it would be unwise to attempt to make a diagnosis of a vascular anomaly in the absence of pyelograms.

If I work on the diagnosis of subacute glomerulonephritis, what have I to go with it? The age at onset, fourteen years, is quite characteristic. In Addis'[1] series the peak age of onset is eight years; 40 per cent of his patients presented between the fifth and the tenth year and 20 per cent between the tenth and the fifteenth year. Although males predominate two to one in most series, the fact that this patient was a girl does not rule against my diagnosis. The type of onset is characteristic. It was sudden, with urinary symptoms but without chills and fever suggestive of infection. The initial episode was short and was followed by a period of latency. This was interrupted by an exacerbation that coincided with the first upper-respiratory infection. Dependent edema, dyspnea and headaches gradually developed. Nephritis with hypertension and edema was first confirmed during a hospital admission elsewhere for an unrelated episode of acute infectious hepatitis. Dependent edema was gradually complicated by ascites and hydrothorax. The patient had persistent hypertension, with eventual cardiac failure, and gradually increasing nitrogen retention culminating in the syndrome of uremia. The entire clinical picture is characteristic of glomerulonephritis, both in its over-all downhill progress and in its punctuation by exacerbations and remissions.

The family history is intensely interesting. This girl has two brothers with what I presume was renal disease, in addition to their hypertension. Although we cannot say that nephritis is a familial disease, I think we can say that an unusual susceptibility to nephritis tends to be present in certain families. Addis[1] lists five families in which there were three siblings affected with the disease. We have had one family in which there were four siblings who had manifestations of the disease before they were ten years of age.

The clinical and laboratory findings recorded during the many admissions here were consistent with chronic glomerulonephritis. As we have seen, the clinical picture was characterized by edema and hypertension. An allergic tendency was demonstrated, in that the patient was sensitive to Diodrast. In the urine, moderate to large quantities of albumin were found, the specific gravity was fixed and granular casts, red cells and white cells were found in the sediment. All the cultures were negative. The serum chemical determinations showed that the patient had the characteristic hypoproteinemia associated with lowering of al-

*Assistant to the Children's Medical Service, Massachusetts General Hospital.

bumin and hypercholesterolemia. Van Slyke[2] has presented evidence to indicate that patients with chronic nephritis do not have a metabolic defect as regards the handling of fat; I think the best explanation that has been offered for the hypercholesterolemia and hyperlipemia seen in these patients is that it is the result of a marked lowering or absence of certain proteins that act as solubilizers of fat.[1] In other words, there may be a difficulty in the transport of fat rather than a defect in its metabolism.

Before I finally commit myself as regards a diagnosis, I might spend a moment on discussion of treatment in this girl. Early in the disease she received a high-protein diet. I believe she was given this diet on the basis of evidence from certain animal experiments.[1, 3, 4] These experiments show that when normal animals or animals whose kidneys are diminished in mass by partial surgical extirpation are given a high-protein diet, the kidneys become markedly hypertrophied. Histologically this hypertrophy has been shown to be due to an increase in the size of the proximal convoluted tubules. There is no increase in the number of nephrons; there is no symmetrical increase in the size of the individual nephrons; there is simply distortion of nephron pattern. I do not think there is any good evidence that such high-protein diets lead to increase of the functional capacity of the kidneys; in fact, it has been shown by Farr and Smadel[5] that in rats with the Masugi type of nephritis there is a much longer period of survival if the rats are fed a low-protein rather than a high-protein diet.

Throughout her course, this patient was treated with a low-salt diet. This, I presume, was given to control hypertension as well as the degree of edema. There is very little evidence in the protocol to indicate that the low-salt diet influenced the hypertension or edema. I should like to mention that on the Children's Metabolic Ward we have put several youngsters with the nephrotic syndrome through ten-day periods of high salt intake. We have been surprised and satisfied to find that although there is a transient gain in weight, comparable to that seen in normal subjects similarly treated, this is followed by a period of diuresis and a return of weight to control levels even while the salt is continued. I think we are becoming less and less convinced that a low-salt diet is a therapeutic "must" in the treatment of patients with the nephrotic syndrome.

Finally, I might comment briefly on the nitrogen-mustard and ACTH treatment that this child was given. Cases of the nephrotic syndrome as seen in young children and of chronic nephritis as seen in older patients have been observed to undergo remission during or at the end of bouts of accidental or induced, nonspecific infections with fever, after induced or acquired measles and after the administration of nitrogen-mustard preparations, ACTH and cortisone. One is tempted to hypothesize that all these agents act through the adrenal gland to modify the ill understood immunologic reactions that are thought to constitute the pathogenesis of glomerulonephritis. Chasis, Goldring and Baldwin[6] were first to demonstrate the effectiveness of nitrogen mustard on certain cases of nephritis in adults; Farnsworth[7] first demonstrated the effectiveness of ACTH in the nephrotic syndrome of children. The evidence is accumulating that fever, measles, ACTH, cortisone and nitrogen mustard are all effective in initiating diuresis in a certain number of cases, especially when administered early in the disease in what the clinicians are beginning to call the reversible phase. If I make any comment here, I think the comment should be that it was too late to expect much effect from ACTH or nitrogen mustard at the time that these agents were used in this case.

I suspect that Dr. Castleman is going to tell us that he found at autopsy, among other things, a kidney lesion consistent with chronic glomerular or pan-nephritis and, secondary thereto, peripheral edema, ascites, hydrothorax, pulmonary edema, cardiac hypertrophy and dilatation, sterile fibrinous pericarditis, myocarditis, hypertensive sclerotic changes in the arterioles, atherosclerosis, superficial ulceration of the pretibial areas with venous thromboses, compensatory hyperparathyroidism and demineralization of bone. In addition, I hope he is going to tell us about the condition of the kidney basement membrane as demonstrated by technics such as those McManus[8] and Ritter[9] have devised for staining this elusive structure.

DR. EDWARD F. BLAND: I happened to be in charge of the ward when this girl came in, desperately ill with acute pulmonary edema. The resident, in addition to other measures, very promptly gave her Mercuhydrin; she lost six pounds of

edema in twenty-four hours, the venous distention lessened and she could breathe again. I think this prompt action postponed the fatal issue for about a year. However, the next day, after the emergency had subsided, he was severely criticized by about half the house staff for having rescued this girl from drowning by the use of Mercuhydrin — theoretically a nephrotoxic drug. I, however, would like to commend his action.

DR. CRAWFORD: I would say that if he could have rescued her with some non-nephrotoxic agent I would have preferred it. On the other hand, I cannot criticize him for having used Mercuhydrin under the circumstances.

DR. BLAND: He saved this girl's life; she lived another year.

DR. CRAWFORD: I would compliment him.

DR. ALLAN BUTLER: I would like to make a comment on that. Perhaps instead of using Mercuhydrin to rescue this girl from the situation of drowning, it might have been prevented by appropriate therapy earlier.

DR. BLAND: She ultimately drowned, however. What would you advise at 3 a.m. under similar circumstances?

DR. BUTLER: I would agree with Dr. Crawford.

CLINICAL DIAGNOSIS

Chronic glomerulonephritis.

DR. CRAWFORD'S DIAGNOSES

Chronic glomerulonephritis.

Anasarca and pulmonary edema.

Cardiac hypertrophy and dilatation.

Sterile fibrinous pericarditis.

Generalized hypertensive arteriosclerosis and atheromatosis.

ANATOMICAL DIAGNOSES

Intracapillary glomerulonephritis.

Calcification and narrowing of coronary, renal, splenic and other arteries.

Nephrocalcinosis.

Cardiac hypertrophy, hypertensive type.

PATHOLOGICAL DISCUSSION

DR. BENJAMIN CASTLEMAN: The autopsy showed a pair of kidneys that were about two thirds the normal size; they were fairly smooth and on microscopical examination, at first glance, appeared like the kidneys that you see in a diabetic — that is, there was lobulation of the glomerular tufts, the so-called intercapillary glomerulosclerosis. Here you see the tuft filled with a hyalin-like material surrounded by the endothelial cells of the capillaries (Fig. 1); every glomerulus was involved in the same fashion. Ordinarily in subacute glomerulonephritis there are many adhesions with crescent formation

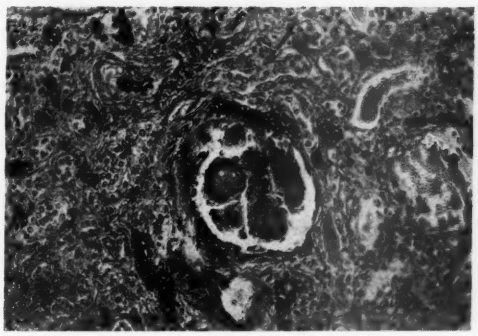

FIGURE 1. *Intracapillary Glomerulonephritis. Note the lobular character of the glomerular tuft and deposits of calcium in tubules and parenchyma (stained black).*

and occasional scarring. Here we were unable to find any adhesions between the glomerulus and its capsule; the glomerular space was free. As I said originally, we thought immediately that this was so-called intercapillary glomerulosclerosis, but there was something a little different about it. We knew that the patient did not have diabetes, but still intercapillary glomerulosclerosis has been seen in nondiabetics. A condition called intracapillary glomerulonephritis, first described by Fahr,[10] was mentioned by Kimmelstiel and Wilson[11] as one that might be difficult to distinguish from intercapillary glomerulosclerosis. Intracapillary, or what Allen[12] calls lobular, glomerulonephritis, is a rare form of glomerulonephritis and is usually associated with the nephrotic picture, and that is what this patient had.

Allen believes that intercapillary glomerulosclerosis is a bad term for the disease observed in diabetics, because he maintains that the disease is

located not between the capillaries but in their walls. These two conditions may be differentiated by a silver stain. A microscopical slide from a case of intercapillary glomerulosclerosis shows thin reticulin fibers surrounding the lobular tufts, in contrast to masses of silver-staining reticulum in curlicue arrangement in the slide of the present case. In the early stages of this form of nephritis there is only marked thickening of the basement membrane of the capillary walls; in the later stages the lobular pattern is seen. It is this basement-membrane alteration that allows for greater permeability and increased urinary albumin. Various lipid stains showed that the convoluted tubules were markedly filled with fat. Lipid droplets, present in the glomerular spaces and in the glomerular arterioles, with the polarizing microscope proved to be cholesterol esters. Scattered through the interstitial tissue were deposits of calcium; some were present in the convoluted tubules.

In addition to the renal changes, the most interesting finding was the marked calcification of the walls of almost all the large and medium-sized arteries throughout the body, apparently associated with the hypercholesterolemia. The coronary arteries were rigid, and their lumens were reduced to pin-point size. Others severely involved were the splenic, renal and uterine arteries and all branches of the celiac axis. There was severe anasarca. The heart was hypertrophied; it weighed 500 gm.

DR. EDGAR TAFT: Do you assume that the calcium formation followed the renal disease as a result of the secondary hyperparathyroidism, or was it part of the disease process?

DR. CASTLEMAN: I do not know that I can answer that. Terminally there was a lot of infection in the kidneys — an acute pyelonephritis, which may lead to foci of calcification; it would not explain all the calcium that was found in the large vessels.

DR. TAFT: Do you think that the kidney calcification could have been seen by x-ray examination?

DR. CASTLEMAN: I would think so; there was a great deal of calcification.

DR. BUTLER: This young lady had two brothers, twenty-four and twenty-two years of age. I think it would be very interesting, unless the Medical Service knows, to find out what has happened to the two brothers and perhaps do some studies on them.

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LET FREEDOM RING

THE current highly publicized "loyalty program," whose tremors are being felt throughout the land of the brave, has been picked up, — a courageous and slightly dangerous action in itself, — by Francis Biddle, for the purpose of examination and a report in a new book, *Fear of Freedom*. The work has been fittingly reviewed by Henry Steele Commager in the *New York Herald Tribune*. Mr. Biddle, it will be recalled, was Attorney General of the United States in 1944 and 1945, and may be accused of the somewhat reprehensible operation of having done some thinking on his own.

Fear of Freedom shows the changed outlook that this country has accepted in the last decade and particularly during these past two oppressive years of the "cold war"; it depicts the great ground swell of reaction to the dread of totalitarian aggression that has already swept away, — only temporarily, it may be hoped, — certain of the fundamental liberties on which the nation's greatness has been based. But the return of any of these liberties and the preservation of the rest can come only through the willingness of Americans of integrity to see the danger and to proclaim it. The alternative is to allow the well-founded fear of Soviet intentions to topple us off the starry heights that we had once attained into our own abyss on the other side.

Great injustices can be done when a confused people succumbs to hysterical guidance or, much worse, follows the direction of sinister fascist elements; the brightest of lights can be dimmed, loyal persons can be persecuted and terror can reign in a democracy as well as elsewhere, if intolerant leadership is allowed to prevail. Such is the burden of *Fear of Freedom*, in which is shown the almost "inevitable progression of the spirit of oppression from suspicion to censorship and from censorship to punishment," with already some very questionable laws engrossed upon the books of various states. A popular form of legislation that has made the Goddess of Bedloe Island tremble a little on her granite base is that making membership in certain organizations a felony punishable by five years' imprisonment.

Other examples of the hazards that lie in this excess of chauvinism are only too plentiful. Witness the case of an employee in a piously managed industry who was accused of "being in sympathy with the underprivileged" and that of another who was "charged with believing that Communists should enjoy the protection of the Constitution"; of still another "it was alleged that Russian songs had been sung in his apartment; a third had to defend his study of the Russian language"! Members of the Broyles Commission in Illinois, it is also reported, have been disturbed over the presence of a life of Paul Robeson in libraries of that state; they have been "concerned about the teaching of anything remotely critical of the American past or of the existing economic system."

This purging from a people of the privilege of expressing its thoughts or even of harboring them has nothing to do with the control of subversive

acts, which is already covered by constitutional laws; it deals rather with "imponderable things like intentions, thoughts, principles and associations, with that shadowy realm which has ever been the happy hunting ground of tyrants."

The risk that this country runs in its flight from reality was once expressed by Benjamin Franklin, who has not yet been accused, so far as is known, of plotting to throw off the yoke of any government except that of his own — although it happened, at the time, to be also that of England. "They that can give up essential liberty," he said, "to obtain a little temporary safety deserve neither liberty nor safety."

As Supreme Court Justice Douglas expressed it, there are rumblings in every village from the Mediterranean to the Pacific that we think of as Communistic but are not; they represent simply a desire for change arising out of a great need, and present a situation that the Communists exploit. Change is indissoluble from progress, without which the spirit dies. When the strength of our national character reasserts itself; when the doubts of its own vitality that democracy now harbors are dispelled — then, it may be hoped, the nation will once again *from every mountain-side Let freedom ring.*

THE ELUSIVE VIRUS

STUDIES like those reported elsewhere in this issue of the *Journal* on the "activation" of herpes simplex and the treatment of herpes zoster have an import far beyond the successful management of a coldsore or shingles. To use a much overworked word, they are "basic" to an improved understanding of viruses affecting the central nervous system and may have applications to problems as far removed from coldsore and shingles as post-pertussis-inoculation encephalitis and poliomyelitis.

The investigation of Carton and Kilbourne adds another specific insult that may "activate" herpetic infection to such well known triggers for coldsore as fever, exposure to sunlight, trauma and intercurrent infections. Observations are recorded on 17 patients subjected to trigeminal-sensory-root section, 16 of whom subsequently developed the vesicular lesions of herpes simplex, usually at the mucocutaneous junction in the area of skin innervated by the severed nerve. In explanation of their findings, Carton and Kilbourne advance the hypothesis that the virus is "activated *in situ* as the result of local changes in tissue metabolism secondary to interference with the sensory innervation of latently infected tissues." An alternative explanation, — so close to the one actually advanced as to be merely a shift in emphasis, — is an increase in susceptibility of the host tissues (the virus remaining stable) subsequent to a localized disturbance brought about by denervation. If increased emphasis is accorded to the host, then the medical counterpart of the surgical phenomenon would be found in the case of the usually light-complexioned person who can count on a coldsore after overenthusiastic exposure to the sun — or the fever blisters that are frequently "activated" by an acute intercurrent febrile illness.

The relation between trigeminal-root section and herpes simplex warrants further intensive study, for more and more in recent years, — and largely as the result of the contributions of the late W. Lloyd Aycock, — greater weight is being given to the role of the host in accounting for epidemic rhythms rather than ascribing all changes in morbidity to increased or decreased virulence of the agent. An increase in virulence was one of the first ready explanations advanced to account for the production of congenital anomalies by the virus of rubella in Australia during 1940–1941, but the passage of time has tended to establish the phenomenon as a manifestation of fetal development (during the first trimester of pregnancy) rather than alteration in the virulence of the virus. Likewise, the relation between infantile paralysis and antecedent tonsillectomy or immunization is clearly a matter of altering the host rather than the infectious agent. The problem of encephalitis following whooping cough also may be indirectly involved, for there is no clear-cut evidence that this disease of the nervous system is not "activated" by the inoculation of hemophilus pertussis rather than directly caused by it.

A question that cannot be easily dismissed comes to mind — whether the virus of herpes simplex could be acting as a causative factor in the produc-

COLLEGE OF AGRICULTURE AND LIBRARY FEB 15 MANHATTAN KANSAS

tion of pain in trigeminal neuralgia. Although the stimulus is generalized to the whole face, when sunburn acts as the trigger for a coldsore, the effect is sharply localized to the area habitually involved. The inference is that the virus has been lurking in the tissues of the affected area all along. If so, where does it reside? Perhaps in nervous tissue. No large proportion of adults is prone to repeated bouts of herpes simplex, and the finding that 16 of 17 patients subjected to operation developed lesions raises the question whether the association between herpes simplex and trigeminal neuralgia might be more than a chance occurrence.

The viruses of herpes zoster and herpes simplex have little more in common, as far as is known, than the capacity to produce vesicular lesions. Although significant host factors have not been proved for herpes zoster, the variations in clinical severity and sites of involvement bespeak their importance. Likewise, the fact that adults are more susceptible than children to herpes zoster is indication of the importance of the host as opposed to the virus. Moreover, the occasional close association in time and place (in families, for example) of cases of shingles with cases of chicken pox suggests the hypothesis that the causative agent of the two diseases may be the same. In the opinion of Pickles,[1] general epidemiologic evidence and his own observations, assembled over a lifelong general practice in an isolated community, in support of this concept are overwhelming:

> In view of the suffering caused by herpes zoster in adults, it would seem to be a great misfortune not to acquire chicken-pox in early life. In 177 patients there were two instances of chicken-pox in adults, but during the same period there were fifty-six instances of herpes zoster or herpes frontalis. The epidemic peaks of the two diseases roughly correspond, but in three epidemics sufferers from herpes appear. . .first and in two epidemics the origin was definitely traced to . . .herpes zoster. The age incidence of infection with the two diseases shows what is well known, that when exposed to the same infecting agent, chicken-pox is more likely to develop in a child and herpes in an adult. I have questioned all the sufferers from herpes, and only one gave me the information that he had suffered from chicken-pox. This patient, a man of 40, had a negligible attack of herpes zoster with slight constitutional upset, but he very definitely infected his small son with chicken-pox, as there was no other possible source of infection.

Interesting cases of the type observed by Pickles were described by Garland in this *Journal* in 1943.[2] Two weeks after a mother had had an eruption typical of herpes zoster, confined to the left side of her face, a son showed scattered papules that developed into well-defined chicken pox. On the following day the husband and the daughter developed chicken pox. Other cases reported in the literature were presented; particularly impressive was an outbreak of chicken pox on a tuberculosis ward, traceable to a patient with herpes zoster. Garland also reviewed the experimental attempts that have been made to inoculate children with fluid from vesicles of herpes zoster: ". . . some subjects developed only local reactions, and some a generalized varicelliform eruption as well."

Despite suggestive evidence, the problem of a monistic etiology for chicken pox and herpes zoster remains unsettled in the opinion of many American clinicians and bacteriologists, and no attempt is made here to beg the final decision. The point is that much essential work on supposedly banal virus infections (shingles, coldsores, chicken pox, warts, rubella) remains to be done in order to establish principles of virus activity and host reactivity that are anything but banal.

References

1. Pickles, W. N. *Epidemiology in Country Practice.* Bristol: John Wright & Sons, Ltd.; London: Simplins Marshall Ltd., 1939. Pp. 46 and 47.
2. Garland, J. Varicella following exposure to herpes zoster. *New Eng. J. Med.* 228:336, 1943.

NORFOLK SOUTH POINTS THE WAY

Norfolk South District Medical Society, the first of the 19 districts of the Massachusetts Medical Society to announce a complete emergency medical-coverage plan, has demonstrated that where there's a will there's a way.

This society, with an active membership of 186 physicians, has now approximately 80, or over 40 per cent of its fellows, participating in the plan to secure for all of the residents of the district adequate medical coverage at all times. This means that through a call to a single number in Quincy, — MAyflower 9-3700, — the urgent needs of patients in Quincy, Braintree, Weymouth, Randolph, Hingham, Cohasset, Holbrook and Hull, comprising the entire district, will be met.

Placards bearing the telephone number and announcing the service, which went into operation

on November 15, 1951, have been distributed to fire and police stations, telephone switchboards, nursing homes, visiting nursing services, physicians' offices and drugstores throughout the district. The fees for the service are the usual ones charged by the physicians of the district, who are meeting the $2.00 per capita per annum charge for maintaining the switchboard.

The success of the plan, however, as announced by its sponsors, will depend on the co-operation of the public as well as of the physicians who have inaugurated it:

> It would be unfair to overload the service with calls that are not genuine emergencies. It does not in any way take the place of existing ambulance and hospital services already provided by police and hospitals in the area. It is not a substitute for having a family physician. It is intended only to cover the unusual situations where a patient cannot find his own physician, or his alternate, in a real crisis.

Already an average of close to three bona-fide emergency calls are handled by the switchboard daily, sufficient evidence of the necessity for the service, much of the credit for which goes to the president of the district society, Dr. Henry F. Howe of Cohasset.

The prestige that the profession of medicine has always tried to guard so jealously has two particularly vulnerable areas. These are in the appearance of commercialism with respect to the fees that are sometimes charged, and of indifference to the needs of the public in failing to provide for the meeting of these needs at all times. Redress for any real overcharge and the investigation of any suspected one can now be obtained by the patient through a complaint to a grievance committee; prompt response to a bona-fide emergency call can be obtained through such co-operative efforts as have been made so successfully by the members of the Norfolk South District Medical Society. Good private relations plus teamwork make the best public relations.

To Correspondents. — A valedictory address, from New Haven, and an account of the post-mortem appearances in a case of Epilepsy, are on file. A reply to one of the articles in last week's Journal, needs some modification before it can be inserted. If controversy is unavoidable, it must at least be divested, in our pages, of offensive personalities.

Boston M. & S. J., *February 4, 1852*

BOSTON MEDICAL LIBRARY

Science Librarians

In the *Library Journal* for November 15, 1951, Mrs. Elizabeth Gilman, librarian of the Langley Aeronautical Library, has an interesting article on science librarians.

Progress in both exact science and applied science, such as medicine, is recorded by a number of means — up-to-date documents, articles in periodicals, monographs and books, to list them in the order of their importance. All these rapidly become outdated. Documents are issued in great numbers in manuscript or printed form — more so in science than in medicine, although with the advent of aeronautic and atomic research they are becoming increasingly important to medical libraries. The periodical articles are usually only a few months behind the times, but their availability depends on prompt listing, which is impossible in the large library because of the great number of periodicals and serials published in all countries of the world. Recourse must be had to the various bibliographical publications, which are necessarily six months to a year out of date because of processing problems. The monograph presents the data on its subject available only some time prior to its publication and is valuable for survey purposes. The textbook is hopelessly out of date when published, as it is usually a couple of years behind the times and can only portray the fundamentals of its subject.

Mrs. Gilman analyzes the present situation concerning science librarians and stresses the immediate need for the training of such personnel. She calls attention to the so-called self-made librarian, — of which she is a notable example, — having no special training but endowed with the knowledge gained through many years' experience on the job. These persons, few in number, cannot be shifted about, and immediate measures must be taken to fill the need for trained librarians.

In this same number of the *Library Journal*, Mr. A. D. Osborn, assistant librarian of the Harvard College Library, has an article on arrearages of cataloguing, which is interesting and encouraging. All progressive libraries giving good service to their clientele are faced with this problem, because of the influx of material, usually regarded as an award for their good service. Some libraries are doubly handicapped by lack of housing space and can make available only late publications and important reference material.

Both these articles may be read with profit by all medical librarians and library trustees.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR DECEMBER, 1951

Résumé

Disease	December 1951	December 1950	Seven-Year Median
Chancroid	4	0	2
Chicken pox	991	1450	1450
Diphtheria	3	10	29
Dog bite	588	656	616
Dysentery, bacillary	0	2	12
German measles	210	50	64
Gonorrhea	162	148	262
Granuloma inguinale	0	1	0
Lymphogranuloma venereum	0	1	1
Malaria	1	0	7
Measles	2685	199	459
Meningitis, meningococcal	10	10	9
Meningitis, Pfeiffer-bacillus	9	3	7
Meningitis, pneumococcal	2	2	4
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	1	1	0
Meningitis, undetermined	5	3	3
Mumps	1314	847	847
Poliomyelitis	9	28	11
Salmonellosis	4	3	5
Scarlet fever	228	387	523
Syphilis	316	112	238
Tuberculosis, pulmonary	137	201	210
Tuberculosis, other forms	6	12	12
Typhoid fever	1	1	2
Undulant fever	2	0	2
Whooping cough	249	363	464

Comment

Diseases noted to be below the seven-year median for December were chicken pox, diphtheria, scarlet fever and whooping cough.

Diseases markedly above the seven-year median were German measles, measles and mumps.

The 3 cases of diphtheria, as well as the 228 cases of scarlet fever, were the lowest number ever recorded for the month of December in Massachusetts. Similarly, 249 cases of whooping cough constitute the lowest number of cases for this disease for the month of December in thirty years.

Of the diseases above the seven-year median, the numbers of cases of German measles and measles were the third highest ever recorded for this month in Massachusetts.

Geographical Distribution of Certain Diseases

Diphtheria was reported from: Boston 2; New Bedford, 1; total, 3.

Encephalitis, infectious, was reported from: Chicopee, 1; West Boylston, 1; Worcester, 1; total, 3.

Hepatitis, infectious, was reported from: Boston, 1; Camp Edwards, 1; Fall River, 2; Haverhill, 1; Newton, 1; Worcester, 9; total, 15.

Lymphocytic choriomeningitis was reported from: Hingham, 1.

Malaria was reported from: Camp Edwards, 1.

Meningitis, meningococcal, was reported from: Auburn, 1; Boston, 2; Cambridge, 1; Chicopee, 1; Lawrence, 1; Natick, 1; Newburyport, 1; Pittsfield, 1; Springfield, 1; total, 10.

Meningitis, Pfeiffer-bacillus, was reported from: Fall River, 1; Greenfield, 1; Holyoke, 1; Lowell, 1; Medford, 1; Milton, 1; Newton, 1; Seekonk, 1; Southwick, 1; total, 9.

Meningitis, pneumococcal, was reported from: Andover, 1; Lynn, 1; total, 2.

Meningitis, streptococcal, was reported from: Wayland, 1.

Meningitis, mumps, was reported from: Boston, 1; Malden, 1; total, 2.

Meningitis, undetermined, was reported from: Lynn, 1; Millbury, 1; Reading, 1; Seekonk, 1; Worcester, 1; total, 5.

Poliomyelitis was reported from: Brookline, 1; Gloucester, 1; Haverhill, 1; Ludlow, 1; Lynn, 1; Somerville, 1; Weston, 1; Wilbraham, 1; Worcester, 1; total, 9.

Salmonellosis was reported from: Boston, 2; Lynn, 1; Millbury, 1; total, 4.

Septic sore throat was reported from: Boston, 5; Warren, 1; total, 6.

Tetanus was reported from: Millbury, 1.

Trichinosis was reported from: Boston, 1; West Springfield, 1; Worcester, 1; total, 3.

Typhoid fever was reported from: Belmont, 1.

Undulant fever was reported from: East Longmeadow, 1; Ware, 1; total, 2.

CORRESPONDENCE

AMERICAN COLLEGE OF SURGEONS

To the Editor: A cordial invitation is extended to your readers to attend a two-day sectional meeting of the American College of Surgeons, to be held at the Chateau Frontenac in Quebec City, Quebec, on February 18 and 19.

Papers, panels and symposia will be presented on current surgical problems. New surgical motion pictures will be shown, including several that were prepared especially for the Cine Clinics at the 1951 Clinical Congress, and a stereoscopic colored film on "Radical Resection for Carcinoma of the Stomach," which is attracting much attention wherever it is shown.

Dr. Paul-A. Poliquin and his committee on arrangements have made extensive preparations to assure a good meeting and a warm welcome to Quebec City for all visiting surgeons. Hotel accommodations may be obtained by writing to Mr. G. J. Jessop, Manager, Chateau Frontenac, Quebec City, Quebec.

H. P. Saunders, M.D.
Associate Director

Chicago, Illinois

A CORRECTION

To the Editor: In the December 13, 1951, issue of the *Journal*, Rose indicated that inadequate credit was accorded his previous work on abdominal intradermal infiltration in labor. I record the following facts:

In the third paragraph of my preliminary report, published in the *Journal* in 1950, before mentioning my own technic I stated: "In 1928 Rose[3] described the successful intradermal use of novocain to break the pain-reference arc in the first stage of labor."* (Reference 3 is: Rose, D. Local anaesthesia in first and second stage labor. *New. Eng. J. Med.* **201**:117-125, 1929. In this, I recognized and stated his priority and referred the interested reader to his report of 1929.

In a film subsequently produced by the Eli Lilly Co. on the subject of "Intradermal Infiltration Anesthesia in the First Stage of Labor," Volume 201 and then Page 117, referred to above, were shown. The narration that accompanied it was as follows: "Infiltration of the skin of the abdomen for the relief of labor pains was first carried out by Rose, who reported his experiences in 1928 and 1929."

Archie A. Abrams, M.D.

Boston, Massachusetts

*Abrams, A. A. Obliteration of pain at site of reference by intradermal infiltration anesthesia in first-stage labor. *New Eng. J. Med.* **243**:636-640, 1950.

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

A Color Atlas of Morphologic Hematologic Hematology: With a guide to clinical interpretation. By Geneva A. Daland, B.S., chief laboratory assistant in hematology, Thorndike Memorial Laboratory, and research laboratory technician, Boston City Hospital. Edited by Thomas H. Ham, M.D., assistant professor of medicine, Harvard Medical School, associate director, Thorndike Memorial Laboratory, and junior visiting physician, Boston City Hospital. 4°, cloth, 74 pp., with 9 illustrations, 14 plates and 12 tables. Cambridge, Massachusetts: Harvard University Press, 1951. $5.00. From the Second and Fourth (Harvard) Medical Services and the Thorndike Memorial Laboratory, Boston City Hospital.

The fourteen full-color plates of this atlas show typical changes of maturation of the blood cells and their appearances in various pathologic conditions. They were made from films of peripheral blood, stained with Wright's stain. Five of the plates are entirely new, and the color work is excellent. A bibliography of 193 titles is appended to the text, and there is a good index. The atlas should be in all collections on the blood.

NOTICES

BOSTON SOCIETY OF BIOLOGISTS

The Boston Society of Biologists will present a symposium on growth mechanisms in the Bigelow Amphitheatre of the Massachusetts General Hospital, on Wednesday, February 13, at 8:00 p.m.

PROGRAM

(Dr. J. C. Aub, Chairman)

The Relation between Cell Enlargement and Metabolism in Plant Tissue — Dr. K. V. Thimann

The Concentration of Amino Acids by the Ehrlich Mouse-Ascites Carcinoma Cell — Dr. H. N. Christensen

Homologous and Heterologous Tumor Growth in the Cheek Pouch of the Hamster (Kodachrome film and discussion) — Dr. B. R. Lutz

Announcements of programs for the remainder of the season will be sent to all who request them. Those who wish to support the Society may contribute $1.00. Suggestions of papers for future meetings are welcome.

SPRINGFIELD ACADEMY OF MEDICINE

The Springfield Academy of Medicine has voted to sponsor the establishment of a rehabilitation center for Springfield. A symposium on this subject will be presented at a meeting on February 12. Speakers will be: Dr. Charles Bradford, chairman of the State Committee on Rehabilitation; Mr. Stanwood Hanson, assistant vice-president of the Liberty Mutual Insurance Company; Dr. J. L. Rudd, chairman of the Department of Physical Medicine of Boston City Hospital; and Dr. Augustus Thorndike, director of rehabilitation at Massachusetts General Hospital.

SPRINGFIELD HOSPITAL

The Educational program of the Springfield Hospital for the month of February is as follows:

February 2
10–11 a.m. Grand Surgical Rounds.
11 a.m.–12 m. Combined Medical-Surgical Grand Rounds with Panel Discussion on the "Management of Bleeding Peptic Ulcer." Discussers: Medical, Dr. Raymond L. Barrett; x-ray, Dr. Robert A. Grugan; and surgical, Dr. W. Fenn Hoyt. Staff Conference Room.

February 6
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

February 9
9–10 a.m. Pathology Conference in the Staff Conference Room. Dr. William Kaufmann.
10–11 a.m. Grand Surgical Rounds.
11 a.m.–12 m. Clinicopathological Conference in the Staff Conference Room.

February 13
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

February 14
12:15 p.m. Staff Meeting in the Staff Room.

February 16
9–10 a.m. Radiology Conference in the Staff Conference Room. Dr. Robert A. Grugan.
10–11 a.m. Grand Surgical Rounds.
11 a.m.–12 m. Medical Death Review in the Staff Conference Room.

February 19
8:30 p.m. Guest Speaker Conference in the Staff Conference Room on the subject "Diseases of the Chest of Infants and Young Children," by Dr. Edward B. D. Neuhauser, radiologist-in-chief, Children's Medical Center, Boston.

February 20
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

February 23
10–11 a.m. Grand Surgical Rounds.
11 a.m.–12 m. Surgical Death Review in the Staff Conference Room.

February 27
11 a.m.–12 m. Psychosomatic Medicine Conference in the Out Patient Department.

NEW ENGLAND SOCIETY OF ANESTHESIOLOGISTS

The New England Society of Anesthesiologists will present a program on "The Physiology of the Respiratory System and Its Relation to Anesthesia," on February 2, as part of its Postgraduate Education Program.

PROGRAM

Physiology of Respiration — Dr. Joseph M. White, assistant professor, Yale University School of Medicine.

Physiology of Ventilation — Lt. James V. Maloney (MC) U.S.N.R. Medical Field Research Laboratory, Camp Lejeune, N. C.

Physiological Considerations of Paradoxical Ventilation — Dr. Thomas S. Lomasney, thoracic surgeon, Providence Veterans Administration Hospital, Providence, Rhode Island.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 1. Symposium on the Diagnosis and Treatment of Cancer of the Lung. Boston City Hospital. Dowling Amphitheatre. 12 noon.
FEBRUARY 2. New England Society of Anesthesiologists. Notice above.
FEBRUARY 2, MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post-Graduate Education Course. Page 966, issue of December 20.
FEBRUARY 2–27. Springfield Hospital. Notice above.
FEBRUARY 4. New England Cardiovascular Society. Page 160, issue of January 24.
FEBRUARY 5–26. Boston City Hospital House Officers' Association. Page 160, issue of January 24.
FEBRUARY 6. Boston City Hospital Fracture Service. Page 114, issue of January 17.
FEBRUARY 6–MARCH 26. Lahey Clinic Fellowship Teaching Program. Page 160, issue of January 24.
FEBRUARY 11 AND 12. American College of Surgeons. Page 160, issue of January 24.
FEBRUARY 12. Springfield Academy of Medicine. Notice above.
FEBRUARY 13. Boston Society of Biologists. Notice above.
FEBRUARY 14. Cancer of the Breast. Dr. Ernest M. Daland. Pentucket Association of Physicians, 8:30 p.m. Haverhill.
FEBRUARY 18 AND 19. American College of Surgeons. Page 203.
FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.
FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.
MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.
MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.
MARCH 24–28. American College of Chest Physicians. Page 160, issue of January 24.
MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.
APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.
APRIL 23. Massachusetts Academy of General Practice. Springfield.
MAY 1–3. American Goiter Association. St. Louis, Missouri.
MAY 20–22. Massachusetts Medical Society. Hotel Statler, Boston.
MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.
JUNE 18–20. Massachusetts Public Health Conference. Amherst.
JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.
JULY 7–12. International Diabetes Federation. Page 997, issue of December 20.
JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.
JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.
SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.
OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

MARCH 5. Cooley-Dickinson Hospital, Northampton.
MAY 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

FEBRUARY 4. Mount Auburn Hospital, Cambridge.
APRIL 30. Hotel Continental, Cambridge.

NORFOLK

FEBRUARY 26. Boston Medical Library.
MARCH 25. Boston Medical Library.
APRIL 22. Boston Medical Library.
MAY 7. Place to be announced.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 7

THURSDAY, FEBRUARY 7
*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheatre, Children's Medical Center.
*4:00–5:00 p.m. Medical Division Lecture. Mount Auburn Hospital, Cambridge.

(*Notices concluded on page xi*)